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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003902015 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 29 April 2003.

WITNESS my hand this
Thirtieth day of October 2003

J. Billingsley

JULIE BILLINGSLEY
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Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

A U S T R A L I A

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Azole Derivatives"

The invention is described in the following statement:

DESCRIPTION

Azole derivatives

Technical Field

This invention relates to azole compounds having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

Background Art

The presence of two cyclooxygenase isoenzymes, cyclooxygenase-I (COX-I) and cyclooxygenase-II (COX-II) is known (Proc. Nat. Acad. Sci. USA 88, 2692-2696 (1991)).

Traditional non steroidal anti-inflammatory compounds (NSAIDs) have inhibiting activities of both COX-I and COX-II (J. Biol. Chem., 268, 6610-6614 (1993), etc). The therapeutic use thereof involves undesired effects on the gastrointestinal tract, such as bleeding, erosions, gastric and intestinal ulcers, etc.

It was reported that selective inhibition of COX-II shows anti-inflammatory and analgesic activities comparable with conventional NSAIDs but with a lower incidence of some gastrointestinal undesired effects (Pro. Nat. Acad. Sci. USA, 91, 3228-3232(1994)). Accordingly, various selective COX-II inhibitors have been prepared. However, it was reported that those "selective COX-II inhibitor" show some side-effects on kidney and/or insufficient efficacy on acute pains.

Further, some compounds such as SC-560, mofezolac, etc, which have certain selective inhibiting activity against COX-I. WO98/57910 shows some compounds having such activity. However, their selectivity of inhibiting COX -I does not seem to be enough to use them as a clinically acceptable and satisfactory analgesic agent due to their gastrointestinal disorders.

WO02/055502 shows some pyridine derivatives having cyclooxygenase

inhibiting activity, particularly cyclooxygenase-I inhibiting activity. And WO99/51580 shows some triazole derivatives having an inhibiting activity of cytokine production.

Disclosure of Invention

This invention relates to azole compounds, which have pharmaceutical activity such as cyclooxygenase (hereinafter described as COX) inhibiting activity, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

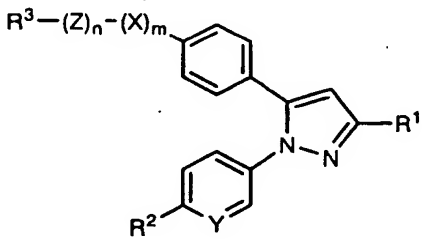
Accordingly, one object of this invention is to provide the azole compounds, which have a COX inhibiting activity.

Another object of this invention is to provide a process for production of the azole compounds.

A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the azole compounds.

Still further object of this invention is to provide a use of the azole compounds for manufacturing a medicament for treating or preventing various diseases.

The new azole compounds of this invention can be represented by the following general formula (I):



(I)

wherein R^1 is (lower)alkyl,
(lower)alkyl substituted with halogen,
(lower)alkyl substituted with hydroxy,
(lower)alkenyl,
(lower)alkoxy,
cycloalkyl,

cyano,
amino,
halogen,
hydroxy,
[di(lower)alkyl]amino,
[(lower)alkoxy]carbonyl,
(lower)alkanoyl,
(cycloalkyl)carbonyl, or
[N,N-di(lower)alkyl]carbamoyl;

R^2 is (lower)alkoxy,
halogen,
(lower)alkyl
(lower)alkyl substituted with amino,
(lower)alkyl substituted with (carbamoyl)amino,
(lower)alkyl substituted with
[(lower)alkyl]sulfonamide,
cyano,
hydroxy,
[aryl(lower)alkyl]oxy,
[(lower)alkanoyl]oxy,
[(lower)alkylene]dioxy,
(lower)alkoxy substituted with hydroxy,
(lower)alkoxy substituted with cyano,
(lower)alkoxy substituted with amino,
(lower)alkoxy substituted with
[(lower)alkoxy]carbonylamino,
(lower)alkoxy substituted with
[(lower)alkyl]sulfonamide, or
(lower)alkoxy substituted with (carbamoyl)amino;

R^3 is hydrogen,
amino,
[(lower)alkokycarbonyl]amino,

[(lower)alkyl]sulfonamide,
(carbamoyl)amino,
aryl,
heteroaryl,
(lower)alkoxy,
hydroxy,
[(lower)alkyl]sulfonyloxy,
(lower)alkyl,
(lower)alkyl substituted hydroxy,
(lower)alkyl substituted with amino,
(lower)alkyl substituted with
[(lower)alkoxycarbonyl]amino,
cyano,
(lower)alkanoyl, or
(lower)alkanoyl substituted with halogen;

X is O, S or (lower)alkylene;

Y is CH or N;

Z is (lower)alkylene, amide or sulfonamide;

m is 0 or 1; and

n is 0 or 1;

or salts thereof.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

So, the "(lower)alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isoamyl, hexyl, and the like, and it is preferably (C1-C4)alkyl, more preferably (C1-C2)alkyl, most preferably methyl.

The "(lower)alkyl substituted with halogen" means a monovalent group in which the above (lower)alkyl is substituted by above halogen atom(s), such as fluoromethyl, chloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, or the like, and it is preferably (C1-C4)alkyl substituted with halogen, more preferably (C1-C2)alkyl substituted with halogen, more preferably (C1-C2)alkyl substituted with fluorine, more preferably methyl substituted with fluorine, most preferably difluoromethyl or trifluoromethyl.

The "(lower)alkyl substituted with hydroxy" means a monovalent group in which the above (lower)alkyl is substituted by a OH group, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 1-hydroxyisopropyl, 2-hydroxyisopropyl, hydroxybutyl, hydroxyisobutyl, hydroxy-tert-butyl, hydroxyhexyl, or the like, and it is preferably (C1-C4)alkyl substituted with hydroxy, more preferably (C1-C3)alkyl substituted with hydroxy.

The "(lower)alkenyl" means a straight or branched chain aliphatic hydrocarbon having more than one double bond between two carbon atom, such as ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, hexenyl, and the like, and it is preferably (C2-C4)alkenyl, more preferably (C2-C3)alkenyl.

The "(lower)alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, or the like, and it is preferably (C1-C4)alkoxy, more preferably (C1-C2)alkoxy, most preferably methoxy.

The "cycloalkyl" means C3-C10 cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, and the like, and it is preferably C3-C6 cycloalkyl, more preferably C3-C5 cycloalkyl, most preferably cyclopropyl.

The "[di(lower)alkyl]amino" means a amino group substituted by the same or different above (lower)alkyl groups, such as dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, dipentylamino, dihexylamino, ethylmethylamino, methylpropylamino, butylmethylamino, ethylpropylamino, butylethylamino, or the like, and it is preferably [di(C1-C4)alkyl]amino, more preferably [di(C1-C4)alkyl]amino, most preferably dimethylamino.

The "[(lower)alkoxy]carbonyl" means a $-CO_2-$[(lower)alkyl] group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, and the like, and it is preferably [(C1-C4)alkoxy]carbonyl, more preferably ethoxycarbonyl.

The "(lower)alkanoyl" means carbonyl group which is substituted by the above (lower)alkyl groups, such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, or the like, and it is preferably (C1-C5)alkanoyl, more preferably (C2-C3)alkanoyl, most preferably acetyl.

The "(cycloalkyl)carbonyl" means a carbonyl group substituted with cycloalkyl group mentioned above, such as cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl, norbornylcarbonyl, adamantylcarbonyl, and the like, and it is preferably [(C3-C6)cycloalkyl]carbonyl, more preferably [(C3-C5)cycloalkyl]carbonyl, most preferably cyclopropylcarbonyl.

The "[N,N-di(lower)alkyl]carbamoyl" means a carbamonyl group substituted with (lower)alkyl group mentioned above, such as dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, dibutylcarbamoyl, diisobutylcarbamoyl, dipentylcarbamoyl, dihexylcarbamoyl, ethylmethylcarbamoyl, methylpropylcarbamoyl, butylmethylcarbamoyl, ethylpropylcarbamoyl, butylethylcarbamoyl, and the like, and it is preferably [di(C1-C4)alkyl]carbamoyl, more preferably [di(C1-C2)alkyl]carbamoyl.

most preferably dimethycarbamoyl.

The "halogen" may include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, and is preferably a fluorine atom or a chlorine atom, more preferably a chlorine atom.

The "(lower)alkyl substituted with amino" means a monovalent group in which the above (lower)alkyl is substituted by a amino group, such as aminomethyl, 2-aminoethyl, aminopropyl, 1-aminoisopropyl, 2-aminoisopropyl, aminobutyl, aminoisobutyl, amino-tert-butyl, aminohexyl, or the like, and it is preferably (C1-C4)alkyl substituted with amino, more preferably (C1-C2)alkyl substituted with amino.

The "(lower)alkyl substituted with (carbamoyl)amino" means a monovalent group in which the above (lower)alkyl is substituted by a (carbamoyl)amino group (urea group), such as carbamoylaminomethyl, 2-(carbamoylamino)ethyl, carbamoylaminopropyl, 1-(carbamoylamino)isopropyl, 2-(carbamoylamino)isopropyl, carbamoylaminobutyl, carbamoylaminoisobutyl, carbamoylamino-tert-butyl, carbamoylaminohexyl, or the like, and it is preferably (C1-C4)alkyl substituted with (carbamoyl)amino, more preferably (C1-C2)alkyl substituted with (carbamoyl)amino.

The "(lower)alkyl substituted with [(lower)alkyl]sulfonamide" means a monovalent group in which the above (lower)alkyl is substituted by a [(lower)alkyl]sulfonamide group, such as methanesulfonamidemthyl, 2-(methanesulfonamide)ethyl, methanesulfonamidepropyl, 1-(methanesulfonamide)isopropyl, 2-(methanesulfonamide)isopropyl, methanesulfonamidebutyl, methanesulfonamideisobutyl, methanesulfonamide-tert-butyl, methanesulfonamidehexyl, or the like, and it is preferably (C1-C4)alkyl substituted with methanesulfonamide, more preferably (C1-C2)alkyl substituted with methanesulfonamide.

The "aryl" means an aromatic hydrocarbon group, such as phenyl, naphtyl, indenyl, or the like, and it is preferably (C6-C10)aryl, more preferably phenyl.

The "[aryl(lower)alkyl]oxy" means a (lower)alkoxy group

substituted with aryl group mentioned above, such as benzyloxy, phenethyloxy, phenylpropyloxy, phenylbutyloxy, naphthylmethyloxy, or the like, and it is preferably [aryl(C1-C4)alkyl]oxy, more preferably [aryl(C1-C2)alkyl]oxy, more preferably [phenyl(C1-C2)alkyl]oxy, most preferably benzyloxy.

The "[(lower)alkanoyl]oxy" means a monovalent group in which oxygen atom is substituted with (lower)alkanoyl group mentioned above, such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, or the like, and it is preferably [(C1-C4)alkanoyl]oxy, more preferably [(C1-C2)alkanoyl]oxy, most preferably acetoxy.

The "(lower)alkylene" means a straight or branched chain aliphatic hydrocarbon divalent group, such as methylene, ethylene, 1-methylethylene, 2-methylethylene, propylene, methylpropylene, butylene, pentylene, hexylene, and the like, and it is preferably (C1-C4)alkylene, more preferably (C1-C2)alkylene.

The "[(lower)alkylene]dioxy" means -O-[(lower)alkylene]-O- group. That is, in this case, R^2 is divalent group and is also substituted at the next carbon atom. This group may be exemplified by methylenedioxy, ethylenedioxy, methylethylenedioxy, propylenedioxy, and the like, and it is preferably [(C1-C4)alkylene]dioxy, more preferably [(C1-C2)alkylene]dioxy, most preferably methylenedioxy.

The "(lower)alkoxy substituted with hydroxy" means a monovalent group in which an oxygen atom is substituted by "(lower)alkoxy substituted with hydroxy" group mentioned above.

The "(lower)alkoxy substituted with cyano" means a monovalent group in which the above (lower)alkoxy is substituted by a cyano group, such as cyanomethoxy, cyanoethoxy, cyanopropoxy, cyanobutoxy, and the like, and it is preferably (C1-C4)alkoxy substituted with cyano, more preferably (C1-C2)alkoxy substituted with cyano, most preferably cyanomethoxy.

The "(lower)alkoxy substituted with amino" means a monovalent group

in which an oxygen atom is substituted by "(lower)alkoxy substituted with amino" group mentioned above.

The "(lower)alkoxyl substituted with [(lower)alkoxycarbonyl]amino" means a (lower)alkoxy substituted with amino group mentioned above substituted with [(lower)alkoxy]carbonyl group mentioned above.

The "(lower)alkoxy substituted with [(lower)alkyl]sulfonamide" means a monovalent group in which an oxygen atom is substituted by "(lower)alkoxy substituted with [(lower)alkyl]sulfonamide" group mentioned above.

The "(lower)alkoxy substituted with (carbamoyl)amino" means a monovalent group in which the above (lower)alkoxy is substituted by a (carbamoyl)amino (urea) group, such as [(carbamoyl)amino]methoxy, [(carbamoyl)amino]ethoxy, [(carbamoyl)amino]propoxy, [(carbamoyl)amino]cyanobutoxy, and the like, and it is preferably (C1-C4)alkoxy substituted with [(carbamoyl)amino], more preferably (C1-C2)alkoxy substituted with [(carbamoyl)amino], most preferably cyanomethoxy.

The "[(lower)alkokycarbonyl]amino" means an amino group substituted with [(lower)alkoky]carbonyl group mentioned above.

The "[(lower)alkyl]sulfonamide" means a sulfonamide group substituted with (lower)alkyl group mentioned above.

The "heteroaryl" means 5-, 6-membered or condensed polycyclic aromatic heterocyclic group which contains at least one hetero atom such as nitrogen, oxygen, sulfur atom. The "heteroaryl" may include 5-membered heteroaryl group such as pyrrolyl, imidazolyl, 1-methyl-1H-imidazolyl, pyrazolyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, or the like; 6-membered heteroaryl group such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, or the like; and condensed polycyclic aryl group such as indolyl, isoindolyl, isoindole-1,3-dione-2-yl, quinolyl, isoquinolyl, benzofuranyl, chromenyl, benzothienyl, or the like; and is preferably condensed

polycyclic aryl group or 5-membered heteroaryl group containing nitrogen atom(s), more preferably isoindole-1,3-dione-2-yl or 1-methyl-1H-imidazolyl.

The "[(lower)alkyl]sulfonyloxy" means a sulfonyloxy group substituted with (lower)alkyl group mentioned above.

The "(lower)alkyl substituted with [(lower)alkoxycarbonyl]amino" means a (lower)alkyl group mentioned above substituted with [(lower)alkoxycarbonyl]amino group mentioned above.

The "(lower)alkanoyl substituted with halogen" means a (lower)alkanoyl group mentioned above substituted with halogen mentioned above, such as trifluoroacetyl, and the like.

The "amide" group in the definition of "Z" may be -NHCO- or -CONH-. Equally, the "sulfonamide" group may be $-SO_2NH-$ or $-NHSO_2-$.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compounds of the formula (I) and its salts can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an

organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

The object compound (I) of the present invention can be prepared by referring to the processes shown in the Examples described later.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

For therapeutic purpose, the analgesic agent of the present invention can be used in a form of pharmaceutical preparation suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like.

Particularly, the analgesic agent of this invention is useful for treating or preventing acute or chronic pains associated with acute or chronic inflammations in human beings or animals by using administered systemically or topically.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

The patents, patent applications and publications cited herein are incorporated by reference.

THE BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are given only for the purpose of illustrating the present invention in more detail.

Example 1-1

(1E)-1-[4-(Methoxymethoxy)phenyl]-4-methyl-1-penten-3-one

1M Sodium hydroxide aqueous solution (5.4ml) was added to a solution of 4-mehoxymethoxybenzaldehyde (4.52g) and 3-methyl-2-butanone (4.69g) in ethanol (27ml), and the mixture was stirred at room temperature overnight.

The mixture partitioned between ethyl acetate and water. The organic layer was washed with water, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography eluted with 10% ethyl acetate/n-hexane to give the title compound (4.03g, 63.2%) as an oil.

1H NMR ($CDCl_3$) : δ 1.18(6H, d, J=6.7Hz), 2.92(1H, m), 3.48(3H, s), 5.21(2H, s), 6.71(1H, d, J=16.0Hz), 7.05(2H, d, J=8.8Hz), 7.51(2H, d, J=8.8Hz), 7.58(1H, d, J=16.0Hz).
MS (ESI+) : m/z 257 (M+Na).

Example 1-2

(1S,2R)- and (1R,2S)-1,2-epoxy-1-[4-(methoxymethoxy)phenyl]-4-methyl-3-pentanone

30% H_2O_2 (1.7ml) and 3M sodium hydroxide aqueous solution (1.7ml) was added to a solution of (1E)-1-[4-(methoxymethoxy)phenyl]-4-methyl-1-penten-3-one obtained by Example 1-1 (2.00g) in ethanol:acetone=3:1 (34ml). The mixture was stirred at room temperature overnight.

The mixture was concentrated in vacuo, and partitioned between

ethyl acetate and water. The organic layer was washed with water, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to give the target compound (2.03g, 95%) as an oil.

1H NMR (DMSO-d6) : δ 1.05(6H, d, J=6.9Hz), 2.85(1H, m), 3.36(3H, s), 3.93(1H, d, J=1.9Hz), 4.00(1H, d, J=1.9Hz), 5.20(2H, s), 7.03(2H, d, J=8.6Hz), 7.30(2H, d, J=8.6Hz).
MS (ESI) : m/z 273 (M+Na).

Example 1-3

4-[3-Isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol

A mixture of (1S,2R)- and (1R,2S)-1,2-epoxy-1-[4-(methoxymethoxy)phenyl]-4-methyl-3-pentanone obtained by Example 1-2 (2.10g) and 4-methoxyphenylhydrazine hydrochloride (1.76g) in ethanol:acetic acid=20:1 (20ml) was stirred at 60℃ for 3hrs.

The mixture was concentrated in vacuo. To the residue was added ethyl acetate and 1M hydrochloric acid. The whole mixture was treated with activated carbon, and was filtered through a celite pad. The filtrate was partitioned. The organic layer was washed successively with 1M hydrochloric acid, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residual solid were collected and washed with ethyl acetate to give the target compound (322.2mg, 12.5%) as a white powder.

1H NMR ($CDCl_3$) : δ 1.33(6H, d, J=7.0Hz), 3.07(1H, m), 3.80(3H, s), 5.18(1H, s), 6.26(1H, s), 6.72(2H, d, J=8.8Hz), 6.83(2H, d, J=9.0Hz), 7.08(2H, d, J=8.8Hz), 7.20(2H, d, J=9.0Hz).
MS (ESI+) : m/z 309 (M+H).

Example 2

tert-Butyl 2-{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

Diethylazodicarboxylate (259mg) was added to a mixture of 4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 1-3 (305mg), 2-t-butoxycarbonylaminoethanol (479mg), and triphenylphosphine (390mg) in tetrahydrofuran (3ml). After stirring at room temperature for 7hrs, diethylazodicarboxylate (17mg) and triphenylphosphine (26mg) was added to the reaction mixture.

After stirring at room temperature for 1hr, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 30% ethyl acetate/n-hexane to give the target compound (396mg, 88.5%) as a solid.

1H NMR ($CDCl_3$) : δ 1.34(6H, d, J=7.0Hz), 1.45(9H, s), 3.07(1H, m), 3.48-3.57(2H, m), 3.80(3H, s), 3.97-4.03(2H, m), 4.97(1H, br-s), 6.26(1H, s), 6.76-6.87(4H, m), 7.14(2H, d, J=8.9Hz), 7.20(2H, d, J=9.0 Hz).

Example 3

2-{4-[3-Isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride

4M Hydrochloric acid/dioxane (2ml) was added to a solution of tert-butyl 2-{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 2 (382mg) in dichloromethane (3ml) at 0℃.

After stirring at room temperature for 1hr, the reaction mixture was concentrated in vacuo. The residue was crystallized from a mixture of isopropanol and ethyl acetate to give the target compound (311mg, 94.7%) as a powder.

1H NMR (DMSO-d6) : δ 1.27(6H, d, J=6.9Hz), 2.95(1H, m), 3.14-3.22(2H, m), 3.76(3H, s), 4.14-4.20(2H, m), 6.41(1H, s), 6.93(4H, d, J=8.9Hz), 7.16(4H, d, J=8.9Hz), 8.22(2H, br-s).

MS (ESI+) : m/z 352 (M+H).

Example 4

N-(2-{4-[3-Isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

Methanesulfonyl chloride (32.2mg) was added to a solution of 2-{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 3 (90.9mg) and triethylamine (71.1mg) in dichloromethane (2ml). The mixture was stirred at room temperature for 2hrs.

The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and a mixture of 1M hydrochloric acid and brine. The aqueous layer was reextracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was crystallized from a mixture of ethyl acetate and isopropylether to give the target compound (78.0mg, 77.5%) as a white powder.

MP : 162-163℃.

1H NMR (DMSO-d6) : δ 1.26(6H, d, J=6.9Hz), 2.94(3H, s), 2.94(1H, m), 3.25-3.39(2H, m), 3.76(3H, s), 3.98-4.04(2H, m), 6.40(1H, s), 6.90(2H, d, J=8.8Hz), 6.93(2H, d, J=8.9Hz), 7.13(2H, d, J=8.8Hz), 7.15(2H, d, J=8.9Hz), 7.27(1H, s).

IR (KBr) : 3122, 2966, 2897, 2871, 1614, 1514cm^{-1}.

Example 5

N-(2-{4-[3-Isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}e

thyl)urea

Trimethylsilylisocyanate (41.4mg) was added to a solution of 2-{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 3 (93.0mg) and triethylamine (72.8mg) in dichloromethane (3ml) and the mixture was stirred at room temperature for 3hrs. Trimethylsilylisocyanate (8.3mg) was added and the mixture was stirred at room temperature for 1.5hrs. Trimethylsilylisocyanate (13.8mg) and triethylamine (12.1mg) was added and the mixture was stirred at room temperature for 1.5hrs.

The mixture was concentrated in vacuo, and the residue was partitioned between chloroform and a mixture of 1M hydrochloric acid and brine. The aqueous layer was extracted with chloroform. The combined organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by 10% methanol/chloroform. The separated silica gel was extracted with 10% methanol/chloroform and the solvent was evaporated in vacuo. The residue was crystallized from a mixture of ethyl acetate and isopropylether to give the target compound (85.7mg, 90.6%) as a white powder.

MP : 100-104℃.

1H NMR (DMSO-d6) : δ 1.26(6H, d, J=6.9Hz), 2.94(1H, m), 3.27-3.36(2H, m), 3.76(3H, s), 3.89-3.96(2H, m), 5.52(2H, s), 6.14(1H, t, J=5.6Hz), 6.39(1H, s), 6.89(2H, d, J=8.7Hz), 6.93(2H, d, J=8.9Hz), 7.12(2H, d, J=8.7Hz), 7.15(2H, d, J=8.9Hz).

IR (KBr) : 3371, 3190, 2964, 2873, 1738, 1684, 1639, 1614, 1543, 1512cm^{-1}.

MS (ESI+) : m/z 395 (M+H).

Example 6

tert-Butyl 2-{4-[3-(1-hydroxy-1-methylethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

tert-Butyl 2-{4-[3-ethoxycarbonyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate (1.37g) in tetrahydrofuran (10ml) was added dropwise to 0.93M solution of methyl magnesium bromide in tetrahydrofuran (16ml) at 24-27℃ with cooling in a water bath.

After stirring at room temperature for 1hr, the mixture was poured into a mixture of saturated aqueous ammonium chloride solution and ice. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 70% ethyl acetate/n-hexane to give the target compound (1.17g, 88%) as an amorphous powder.

MS (ESI+) : m/z 468(M+H)

1H NMR ($CDCl_3$) : δ 1.45(9H, s), 1.65(6H, s), 2.78(1H, s), 3.48-3.57(2H, m), 3.81(3H, s), 3.97-4.03(2H, m), 4.97(1H, br), 6.36(1H, s), 6.78-6.89(4H, m), 7.13(2H, d, J=8.7Hz), 7.21(2H, d, J=8.9Hz).

Example 7

tert-Butyl 2-{4-[3-isopropenyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

Methanesulfonyl chloride (367mg) and triethylamine (649mg) were added successively to a solution of tert-butyl 2-{4-[3-(1-hydroxy-1-methylethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 6 (1.0g) and N,N-dimethylformamide (91.5mg) in dichloromethane (10ml) and the mixture was stirred at room temperature for 2hrs. Additional methanesulfonyl chloride and triethylamine were added until all starting material was consumed with

stirring at the same temperature.

The reaction mixture was partitioned between ethyl acetate and 1M hydrochloric acid, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 30% ethyl acetate/n-hexane to give the target compound (900mg, 93.6%) as an amorphous powder.

1H NMR ($CDCl_3$) : δ 1.45(9H, s), 2.21(3H, s), 3.48-3.57(2H, m), 3.81(3H, s), 3.97-4.03(2H, m), 4.98(1H, br-s), 5.12(1H, br-s), 5.59(1H, br-s), 6.56(1H, s), 6.77-6.87(4H, m), 7.14(2H, d, J=8.7Hz), 7.22(2H, d, J=8.9Hz).

MS (ESI+) : m/z 450 (M+H).

Example 8

tert-Butyl 2-{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

A mixture of 10% Pd-C 50% wet (65mg) and tert-butyl 2-{4-[3-isopropenyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 7 (645mg) in tetrahydrofuran (2ml) and methanol (4ml) was hydrogenated under H_2 1atm at room temperature for 3hrs.

The catalyst was removed by filtration. The filtrate and combined washings were concentrated in vacuo. The residue was crystallized from a mixture of ethyl acetate and isopropylether to give the target compound (370mg, 57.1%) as a white powder.

1H NMR ($CDCl_3$) : δ 1.34(6H, d, J=7.0Hz), 1.45(9H, s), 3.07(1H, m), 3.48-3.57(2H, m), 3.80(3H, s), 3.97-4.03(2H, m), 4.97(1H, br-s), 6.26(1H, s), 6.76-6.87(4H, m), 7.14(2H, d, J=8.9Hz), 7.20(2H, d, J=9.0Hz).

MS (ESI+) : m/z 452 (M+H).

Example 9

tert-Butyl 2-{4-[3-(1-hydroxy-1-methylethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (624.4mg, 42.9%) was prepared as an amorphous powder from tert-butyl 2-{4-[3-(1-hydroxy-1-methylethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate in a similar manner to that of Example 6.

1H NMR ($CDCl_3$) : δ 1.45(9H, s), 1.65(6H, s), 3.49-3.57(3H, m), 3.93(3H, s), 3.98-4.04(2H, m), 4.98(1H, br), 6.39(1H, s), 6.72(1H, d, J=8.8Hz), 6.83(2H, d, J=8.8Hz), 7.15(2H, d, J=8.8Hz), 7.54(1H, dd, J=2.8, 8.8Hz), 8.07(1H, d, J=2.8Hz).
MS(ESI+) : 469 (M+H).

Example 10

tert-Butyl 2-{4-[3-isopropenyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (495mg, 85.7%) was prepared as an oil from tert-butyl 2-{4-[3-(1-hydroxy-1-methylethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 9 in a similar manner to that of Example 7.

1H NMR ($CDCl_3$) : δ 1.45(9H, s), 2.20(3H, s), 3.49-3.57(2H, m), 3.92(3H, s), 3.98-4.04(2H, m), 4.99(1H, br-s), 5.15(1H, br-s), 5.60(1H, br-s), 6.58(1H, s), 6.72(1H, d, J=8.8Hz), 6.83(2H, d, J=8.7Hz), 7.15(2H, d, J=8.7Hz), 7.55(1H, dd, J=2.6, 8.8Hz), 8.09(1H, d, J=2.6Hz).

MS (ESI+) : m/z 451 (M+H).

Example 11

tert-Butyl 2-{4-[3-isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (220mg, quant.) was prepared as an amorphous powder from tert-butyl 2-{4-[3-isopropenyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 10 in a similar manner to that of Example 8.

1H NMR ($CDCl_3$) : δ 1.34(6H, d, J=6.8Hz), 1.45(9H, s), 3.07(1H, m), 3.48-3.57(2H, m), 3.92(3H, s), 3.98-4.04(2H, m), 4.98(1H, br), 6.28(1H, s), 6.71(1H, d, J=8.9Hz), 6.82(2H, d, J=8.9Hz), 7.14(2H, d, J=8.9Hz), 7.56(1H, dd, J=2.6, 8.9Hz), 8.05(1H, d, J=2.6Hz).
MS (ESI+) : m/z 453 (M+H).

Example 12

2-{4-[3-Isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanamine dihydrochloride

The title compound (257mg, quant.) was prepared as an amorphous powder from tert-butyl 2-{4-[3-isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 11 in a similar manner to that of Example 3.

1H NMR (DMSO-d6) : δ 1.27(6H, d, J=6.9Hz), 2.96(1H, m), 3.15-3.23(2H, m), 3.85(3H, s), 4.15-4.21(2H, m), 6.47(1H, s), 6.86(1H, d, J=8.8Hz), 6.97(2H, d, J=8.8Hz), 7.20(2H, d, J=8.8Hz), 7.62(1H, dd, J=2.7, 8.8Hz), 8.01(1H, d, J=2.7Hz), 8.19(2H, s).
MS (ESI+) : m/z 353 (M+H).

Example 13

N-(2-{4-[3-Isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (49.9mg, 51.6%) was prepared as a white powder from 2-{4-[3-isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanamine obtained by Example 12 in a similar manner to that of Example 5.

MP : 106-107℃.

1H NMR (DMSO-d6) : δ 1.27(6H, d, J=6.9Hz), 2.96(1H, m), 3.27-3.36(2H, m), 3.85(3H, s), 3.94(2H, t, J=5.5Hz), 5.52(2H, s), 6.15(1H, t, J=5.6Hz), 6.45(1H, s), 6.85(1H, d, J=8.8Hz), 6.93(2H, d, J=8.7Hz), 7.16(2H, d, J=8.7Hz), 7.60(1H, dd, J=2.6, 8.8Hz), 8.02(1H, d, J=2.6 Hz).

IR (KBr) : 3400, 3390, 3379, 3352, 2960, 1657, 1608, 1547, 1512, 1500cm^{-1}.

MS (ESI+) : m/z 396 (M+H).

Example 14-1

5-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-amine

Sodium (3.19g) was added portionwise to ethanol (160ml). After all sodium was dissolved, 4-methoxyphenylhydrazine hydrochloride (14.5g) was added in one portion to the solution. The mixture was stirred at room temperature for 10min. To this mixture was added 3-(4-benzyloxyphenyl)acrylonitrile (16.3g) in one portion, and the mixture was refluxed for 3days.

Insoluble matter was filtered off, and the filtrate was concentrated in vacuo. Ethyl acetate and water were added to the residue and the mixture was stirred at room temperature for 1hr. Precipitates were

collected and washed successively with water, ethyl acetate, and air dried to give the target compound (12.57g, 48.6%) as a powder.

1H NMR (DMSO-d6) : δ 2.49(1H, dd, J=8.3, 16.1Hz), 3.29(1H, dd, J=10.2, 16.1Hz), 3.60(3H, s), 4.69(1H, dd, J=8.3, 10.2Hz), 5.06(2H, s), 5.62(2H, s), 6.65(4H, s), 6.97(2H, d, J=8.6Hz), 7.25(2H, d, J=8.6Hz), 7.31-7.48(5H, m).

MS : (ESI+) : m/z 374 (M+H).

Example 14-2

5-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-amine

MnO_2 (3.5g) was added to a solution of 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-amine obtained by Example 14-1 (12.54g) in N,N-dimethylformamide (65ml) and the mixture was stirred at 60℃ for 2hrs. MnO_2 (5.3g) was added and the mixture was stirred at 60℃ for 1hr.

The mixture was filtered through a celite pad and the pad was washed with N,N-dimethylformamide. To the filtrate were added ethyl acetate and water, and the mixture was stirred at room temperature for 1hr. Precipitates were collected and washed with water and air dried. The obtained powder was suspended in hot isopropylether cooled with stirring, collected and washed with isopropylether to give the target compound (11.70g, 93.8%) as a powder.

1H NMR (DMSO-d6) : δ 3.74(3H, s), 4.84(2H, s), 5.08(2H, s), 5.73(1H, s), 6.87(2H, d, J=9.0Hz), 6.96(2H, d, J=9.0Hz), 7.03-7.13(4H, m), 7.34-7.47(5H, m).

MS (ESI+) : m/z 372 (M+H).

Example 15

5-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-N,N-dimethyl-1H-pyrazo

l-3-amine

37% Aqueous formamide solution (6ml) and sodium cyanoborohydrid e (1.39g) were added successively to a solution of 5-[4-(benzyloxy) phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-amine obtained by Example 14-2 (2.75g) in methanol 30ml. The reaction mixture was stirred at room temperature for 3days, occasionally adding 37% aqueous formam ide solution and sodium cyanoborohydride appropriate amount to cons ume all starting material.

The reaction mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 20% ethyl acetate/chloroform to give the target compound (0.88g, 29.8%) as an oil.

1H NMR (DMSO-d6) : δ 2.81(6H, s), 3.75(3H, s), 5.08(2H, s), 6.03(1H, s), 6.90(2H, d, J=8.9Hz), 6.97(2H, d, J=8.8Hz), 7.06-7.16(4H, m), 7.32-7.46(5H, m).
MS (ESI+) : m/z 400 (M+H).

Example 16

4-[3-(Dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol

A mixture of 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-N,N-d imethyl-1H-pyrazol-3-amine obtained by Example 15 (0.83g) and 10% P d-C 50% wet (160mg) in acetic acid (8ml) was hydrogenated under H_2 1 atm at room temperature for 10hrs.

The catalyst was removed by filtration. The filtrate and combined washings were concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 20% ethyl acetate/chloroform and

was crystallized from a mixture of isopropylether and ethyl acetate to give the target compound (455mg, 70.8%) as a white powder.

1H NMR (DMSO-d6) : δ 2.80(6H, s), 3.74(3H, s), 5.96(1H, s), 6.69(2H, d, J=8.5Hz), 6.89(2H, d, J=9.0Hz), 7.01(2H, d, J=8.5Hz), 7.09(2H, d, J=9.0Hz), 9.64(1H, s).
MS (ESI+) : m/z 310 (M+H).

Example 17

tert-Butyl 2-{4-[3-(dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (477.1mg, 99.7%) was prepared as an oil from 4-[3-(dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 16 in a similar manner to that of Example 2.

1H NMR ($CDCl_3$) : δ 1.45(9H, s), 2.93(6H, s), 3.48-3.54(2H, m), 3.79(3H, s), 3.97-4.03(2H, m), 4.97(1H, br), 5.85(1H, s), 6.79(2H, d, J=8.7Hz), 6.81(2H, d, J=9.0Hz), 7.10-7.27(4H, m).

Example 18

5-[4-(2-Aminoethoxy)phenyl]-1-(4-methoxyphenyl)-N,N-dimethyl-1H-pyrazol-3-amine hydrochloride

The title compound (454mg, quant.) was prepared as an amorphous from tert-butyl 2-{4-[3-(dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 17 in a similar manner to that of Example 3.

1H NMR (DMSO-d6) : δ 2.83(6H, s), 3.16-3.25(2H, m), 3.75(3H, s), 4.13-4.18(2H, m), 6.06(1H, s), 6.91(2H, d, J=9.0Hz), 6.94(2H, d, J=8.8Hz), 7.12(2H, d, J=9.0Hz), 7.17(2H, d, J=8.8Hz), 8.05(2H, br-s).

MS (ESI+) : m/z 353 (M+H).

Example 19

N-(2-{4-[3-(Dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (116mg, 55.7%) was prepared as an amorphous from 5-[4-(2-aminoethoxy)phenyl]-1-(4-methoxyphenyl)-N,N-dimethyl-1H-pyrazol-3-amine hydrochloride obtained by Example 18 in a similar manner to that of Example 75 described later.

1H NMR (DMSO-d6) : δ 2.81(6H, s), 3.29-3.34(2H, m), 3.74(3H, s), 3.92(2H, t, J=5.6Hz), 5.53(2H, s), 6.03(1H, s), 6.15(1H, t, J=5.6Hz), 6.88-6.92(4H, m), 7.04-7.14(4H, m).

IR (neat) : 3344, 3330, 3321, 1658, 1651, 1643, 1612, 1579, 1564, 1554, 1529, 1514cm^{-1}.

MS (ESI+) : m/z 396 (M+H).

Example 20-1

5-[4-(Methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-amine

The title compound (4.0g, 57.8%) was prepared as a powder from 3-(4-methoxymethoxyphenyl)acrylonitrile in a similar manner to that of Example 14-1.

1H NMR (DMSO-d6) : δ 2.49(1H, dd, J=8.3, 16.1Hz), 3.30(1H, dd, J=10.3, 16.1Hz), 3.36(3H, s), 3.59(3H, s), 4.70(1H, dd, J=8.3, 10.3Hz), 5.16(2H, s), 5.62(2H, s), 6.65(4H, s), 6.97(2H, d, J=8.6Hz), 7.25(2H, d, J=8.6Hz).

MS (ESI+) : m/z 328 (M+H).

Example 20-2

5-[4-(Methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-amin
e

The title compound (4.80g, quant.) was prepared as an oil from 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-4,5-dihydro-1H-py razol-3-amine obtained by Example 20-1 in a similar manner to that of Example 14-2..

1H NMR (DMSO-d6) : δ 3.36(3H, s), 3.74(3H, s), 4.85(2H, s), 5.18(2H, s), 5.74(1H, s), 6.88(2H, d, J=9.0Hz), 6.96(2H, d, J=8.8Hz), 7.02-7.13(4H, m).
MS (ESI+) : m/z 326 (M+H).

Example 21

3-Chloro-5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyraz ole

A mixture of 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-amine obtained by Example 20-2 (3.79g), lithium chlori de (2.47g), and copper(II) chloride (3.13g) in acetonitrile (60ml) was stirred at room temperature for 10min. To this mixture was adde d isoamyl nitrite (2.73g), and the mixture was stirred at room temp erature for 1hr.

The mixture was partitioned between ethyl acetate and saturated aqueous ammonium chloride solution. The organic layer was washed with saturated aqueous ammonium chloride solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 30% ethyl acetate/n-hexane. The solvent was evaporated in vacuo. The residue was crystallized from a mixture of isopropylether and ethyl acetate to give the target compound (2.38g, 59.3%) as a white powder.

1H NMR ($CDCl_3$) : δ 3.48(3H, s), 3.82(3H, s), 5.17(2H, s), 6.36(1H, s), 6.85(2H, d, J=9.0Hz), 6.95(2H, d, J=8.9Hz), 7.12(2H, d, J=8.9Hz), 7.20(2H, d, J=9.0Hz).

MS (ESI+) : m/z 345(M+H).

Example 22

4-[3-Chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol

To a solution of 3-chloro-5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazole obtained by Example 21 (2.35g) in tetrahydrofuran (10ml) and methanol (10ml) was added 36% hydrochloric acid (0.34ml). The reaction mixture was stirred at room temperature for 1hr, at 50℃ for 1.5hrs, and at 60℃ for 1.5hrs.

The mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue solid was collected and washed with a mixture of isopropylether and n-hexane to give the target compound (1.99g, 97.1%) as a white powder.

1H NMR (DMSO-d6) : δ 3.78(3H, s), 6.62(1H, s), 6.71(2H, d, J=8.7Hz), 6.96(2H, d, J=9.0Hz), 7.03(2H, d, J=8.7Hz), 7.19(2H, d, J=9.0Hz), 9.80(1H, s).

200MHz 1H NMR ($CDCl_3$) : δ 3.82(3H, s), 5.24(1H, s), 6.35(1H, s), 6.75(2H, d, J=8.6Hz), 6.84(2H, d, J=9.0Hz), 7.07(2H, d, J=8.6Hz), 7.18(2H, d, J=9.0Hz).

MS (ESI+) : m/z 301 (M+H).

Example 23

2-{4-[3-Chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanol

Sodium hydride 60% dispersion in mineral oil (31.1mg) was added to a solution of 4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 22 (180mg) in N,N-dimethylformamide (2ml) under cooling in an ice bath. The reaction mixture was stirred at room temperature for 1hr. To the reaction mixture was added a solution of 2-bromoethyl tert-butyl(dimethyl)silyl ether (258mg) in N,N-dimethylformamide (2ml).

After stirring at room temperature overnight, the mixture was poured into ice water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in ethanol (3.6ml). To this solution was added 36% aqueous hydrochloric acid (0.3ml). After stirring at room temperature for 3 hrs, the mixture was concentrated in vacuo. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by 70% ethyl acetate/n-hexane. The separate silica gel was extracted with 10% methanol/chloroform and the solvent was evaporated in vacuo. The residue was crystallized from a mixture of isopropylether and ethyl acetate to give the target compound (136.4mg, 66.1%) as a white powder.

MP : 114.7-115.5℃.

1HNMR(DMSO-d6) : δ 3.64-3.73(2H,m), 3.77(3H,s), 3.97(2H,t,J=4.9Hz), 4.86(1H, t, J=5.4Hz), 6.68(1H, s), 6.91(2H, d, J=8.9Hz), 6.96(2H, d, J=8.9Hz), 7.15(2H, d, J=8.9Hz), 7.20(2H, d, J=8.9Hz).

IR(KBr) : 3521, 1610, 1518cm^{-1}.

MS (ESI+) : m/z 345 (M+H).

Example 24

tert-Butyl 2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (329.5mg, 22.3%) was prepared as an amorphous from 4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 22 in a similar manner to that of Example 73 described later.

1H NMR ($CDCl_3$) : δ 1.45(9H, s), 3.48-3.57(2H, m), 3.81(3H, s), 4.00(2H, t, J=5.1Hz), 4.96(1H, br), 6.35(1H, s), 6.81(2H, d, J=8.8Hz), 6.84(2H, d, J=8.9Hz), 7.12(2H, d, J=8.8Hz), 7.18(2H, d, J=8.9Hz).
MS (ESI+) : m/z 444 (M+H).

Example 25

tert-Butyl 2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (1.31g, 97.8%) was prepared from 4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 22 in a similar manner to that of Example 2.

MS (ESI+) : m/z 444 (M+H).

Example 26

2-{4-[3-Chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride

The title compound (605.2mg, 85.4%) was prepared as a white powder from tert-butyl 2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 25 in a similar manner to that of Example 3.

1H NMR (DMSO-d6) : δ 3.14-3.23(2H, m), 3.78(3H, s), 4.14-4.20(2H, m), 6.70(1H, s), 6.96(2H, d, J=8.8Hz), 6.97(2H, d, J=8.9Hz), 7.19(2H, d, J=8.8Hz), 7.21(2H, d, J=8.9Hz), 8.19(2H, br-s).

MS (ESI+) : m/z 344 (M+H).

Example 27

N-(2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (137.8mg, 82.8%) was prepared as a white powder from 2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 26 in a similar manner to that of Example 4.

MP : 117-119℃.

1H NMR (DMSO-d6) : δ 2.94(3H, s), 3.27-3.34(2H, m), 3.76(3H, s), 4.02(2H, t, J=5.5Hz), 6.69(1H, s), 6.90-7.01(4H, m), 7.14-7.25(4H, m), 7.28(1H, t, J=5.7Hz).

IR (KBr) : 1612, 1516cm^{-1}.

MS (ESI+) : m/z 422(M+H).

Example 28

N-(2-{4-[3-Chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (174.6mg, 85.8%) was prepared as a white powder from 2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 26 in a similar manner to that of Example 75 described later.

MP : 144.8-145.4℃.

1HNMR(DMSO-d6) : δ 3.27-3.34(2H, m), 3.77(3H, s), 3.93(2H, t, J=5.5Hz), 5.52(2H, s), 6.15(1H, t, J=5.7Hz), 6.68(1H, s), 6.92(2H, d, J=9.0Hz), 6.97(2H, d, J=9.0Hz), 7.15(2H, d, J=9.0Hz), 7.20(2H, d, J=9.0Hz).
IR (ATR) : 3423, 3402, 3203, 3143, 3010, 2976, 2943, 2885, 1651, 1610, 1583, 1516cm^{-1}.
MS (ESI+) : m/z 387 (M+H).

Example 29-1
5-[4-(Methoxymethoxy)phenyl]-1-(6-methoxy-3-pyridinyl)-4,5-dihydro-1H-pyrazol-3-amine

The title compound (1.63g, 41.2%) was prepared as a powder from 3-(4-methoxymethoxyphenyl)acrylonitrile and 2-methoxy-5-pyridinyl hydrazine dihydrochloride in a similar manner to that of Example 14-1.

H NMR (DMSO-d6) : δ 2.48-2.60(1H, dd, overlapping), 3.23-3.34(1H, dd, overlapping), 3.36(3H, s), 3.68(3H, s), 4.75(1H, dd, J=8.6, 10.0Hz), 5.16(2H, s), 5.77(2H, s), 6.56(1H, d, J=8.8Hz), 6.98(2H, d, J=8.6Hz), 7.15(1H, dd, J=2.8, 8.8Hz), 7.27(2H, d, J=8.6Hz), 7.49(1H, d, J=2.8Hz).
MS (ESI+) : m/z 329 (M+H).

Example 29-2
5-[4-(Methoxymethoxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-3-amine

The title compound (1.77g, quant.) was prepared as an oil from 5-[4-(methoxymethoxy)phenyl]-1-(6-methoxy-3-pyridinyl)-4,5-dihydro-1H-pyrazol-3-amine obtained by Example 29-1 in a similar manner to that of Example 14-2.

1H NMR (DMSO-d6) : δ 3.37(3H, s), 3.83(3H, s), 4.97(2H, s), 5.19(2H,

s), 5.78(1H, s), 6.81(1H, d, J=8.9Hz), 6.99(2H, d, J=8.8Hz), 7.15(2H, d, J=8.8Hz), 7.51(1H, dd, J=2.7, 8.9Hz), 7.92(1H, d, J=2.7Hz).
MS (ESI+) : m/z 327 (M+H).

Example 30

5-{3-Chloro-5-[4-(methoxymethoxy)phenyl]-1H-pyrazol-1-yl}-2-methoxypyridine

The title compound (981.7mg, 57.9%) was prepared as a powder from 5-[4-(methoxymethoxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-3-amine obtained by Example 29-2 in a similar manner to that of Example 21.

1H NMR ($CDCl_3$) : δ 3.48(3H, s), 3.93(3H, s), 5.18(2H, s), 6.39(1H, s), 6.74(1H, d, J=8.8Hz), 6.99(2H, d, J=8.8Hz), 7.13(2H, d, J=8.8Hz), 7.55(1H, dd, J=2.7, 8.8Hz), 8.05(1H, d, J=2.7Hz).
MS (ESI+) : m/z 346 (M+H).

Example 31

4-[3-Chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol

The title compound (2.15g, 80.5%) was prepared as a white powder from 5-{3-chloro-5-[4-(methoxymethoxy)phenyl]-1H-pyrazol-1-yl}-2-methoxypyridine obtained by Example 30 in a similar manner to that of Example 22.

1H NMR (DMSO-d6) : δ 3.87(3H, s), 6.68(1H, s), 6.74(2H, d, J=8.6Hz), 6.89(1H, d, J=8.8Hz), 7.07(2H, d, J=8.6Hz), 7.65(1H, dd, J=2.7, 8.8Hz), 8.09(1H, d, J=2.7Hz), 9.86(1H, br-s).
MS (ESI+) : m/z 302 (M+H).

Example 32

2-{4-[3-Chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanol

The title compound (140.9mg, 86%) was prepared as a white powder from 4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol obtained by Example 31 in a similar manner to that of Example 23.

MP : 136.5-138.2℃.
1H NMR (DMSO-d6) : δ 3.65-3.74(2H, m), 3.87(3H, s), 3.98(2H, t, J=4.9Hz), 4.87(1H, t, J=5.5Hz), 6.74(1H, s), 6.86-6.98(3H, m), 7.19(2H, d, J=8.8Hz), 7.67(1H, dd, J=2.8, 8.8Hz), 8.10(1H, d, J=2.8Hz).
IR (KBr) : 3369, 2960, 1610, 1502cm^{-1}.
MS (ESI+) : m/z 346 (M+H).

Example 33
tert-Butyl 2-{4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (964mg, 93.4%) was prepared as a white solid from 4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol obtained by Example 31 in a similar manner to that of Example 2.

1H NMR (DMSO-d6) : δ 1.37(9H, s), 3.22-3.33(2H, m), 3.87(3H, s), 3.95(2H, t, J=5.7Hz), 6.74(1H, s), 6.86-7.04(4H, m), 7.19(2H, d, J=8.7Hz), 7.67(1H, dd, J=2.7, 8.8Hz), 8.11(1H, d, J=2.7Hz).
MS (ESI+) : m/z 445 (M+H).

Example 34
2-{4-[3-Chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanamine dihydrochloride

The title compound (842mg, 98.6%) was prepared as an amorphous

from tert-butyl 2-{4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazo l-5-yl]phenoxy}ethylcarbamate obtained by Example 33 in a similar m anner to that of Example 3.

1H NMR (DMSO-d6) : δ 3.15-3.24(2H, m), 3.87(3H, s), 4.19(2H, t, J=4. 9Hz), 6.76(1H, s), 6.90(1H, d, J=8.8Hz), 6.99(2H, d, J=8.8Hz), 7.23 (2H, d, J=8.8Hz), 7.68(1H, d, J=2.7, 8.8Hz), 8.10(1H, d, J=2.7Hz), 8.20(2H, br-s).
MS (ESI+) : m/z 345 (M+H).

Example 35

N-(2-{4-[3-Chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenox y}ethyl)urea

The title compound (119.5mg, 62.4%) was prepared as a white pow der from 2-{4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl] phenoxy}ethanamine dihydrochloride obtained by Example 34 in a simi lar manner to that of Example 75 described later.

MP : 155.6-157.9℃.
1H NMR (DMSO-d6) : δ 3.27-3.34(2H, m), 3.87(3H, s), 3.94(2H, t, J=5. 5Hz), 5.53(2H, s), 6.15(1H, t, J=5.5Hz), 6.75(1H, s), 6.89(1H, d, J =8.8Hz), 6.95(2H, d, J=8.8Hz), 7.19(2H, d, J=8.8Hz), 7.66(1H, dd, J =2.7, 8.8Hz), 8.11(1H, d, J=2.7Hz).
IR (KBr) : 3425, 3415, 3319, 1657, 1610, 1591, 1581, 1574, 1500cm^{-1}.

Example 36

5-[4-(Benzyloxy)phenyl]-3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazo le

A mixture of 5-[4-(benzyloxy)phenyl]-3-hydroxy-1-(4-methoxyphe nyl)-1H-pyrazol (2.4g), 2-iodopropane (5.48g), and potassium carbon

ate (2.67g) in N,N-dimethylformamide (10ml) was stirred at 100℃ fo r 3hrs.

The reaction mixture was poured into ice water and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 20% ethyl acetate/n-hexane and the solvent was evaporated in vacuo. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give the target compound (2.14g, 80.1%) as a white powder.

1H NMR (DMSO-d6) : δ 1.31(6H, d, J=6.1Hz), 3.76(3H, s), 4.75(1H, m), 5.08(2H, s), 6.00(1H, s), 6.92(2H, d, J=9.0Hz), 6.97(2H, d, J=8.9Hz), 7.10-7.16(4H, m), 7.34-7.43(5H, m).

MS (ESI+) : m/z 415 (M+H).

Example 37

4-[3-Isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol

To a solution of ammonium formate (954mg) in water (2ml) were added ethanol (10ml), a solution of 5-[4-(benzyloxy)phenyl]-3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazo le obtained by Example 36 (2.09g) in tetrahydrofuran (10ml), and 10% palladium on carbon 50% wet (200mg) successively. The mixture was refluxed for 1hr.

The catalyst was removed by filtration and washed with ethyl acetate. The filtrate and combined washings were concentrated in vacuo. Ethyl acetate and water were added to the residue. Precipitates were collected and washed with water and ethyl acetate to give the first crop of the target compound (419mg) as a white powder. The filtrate was partitioned, and the organic layer was saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue

crystals were collected and washed with isopropylether to give the second crop of the target compound (1.19g, 72.5%) as a white powder.

1H NMR (DMSO-d6) : δ 1.31(6H, d, J=6.2Hz), 3.75(3H, s), 4.75(1H, m), 5.93(1H, s), 6.70(2H, d, J=8.6Hz), 6.91(2H, d, J=9.0Hz), 7.01(2H, d, J=8.6Hz), 7.11(2H, d, J=9.0Hz), 9.70(1H, s).
MS (ESI+) : m/z 325(M+H).

Example 38

2-{4-[3-Isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanol

The title compound (147.3mg, 88.2%) was prepared as an oil from 4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 37 in a similar manner to that of Example 23.

1H NMR ($CDCl_3$) : δ 1.40(6H, d, J=6.2Hz), 2.02(1H, t, J=5.8Hz), 3.79(3H, s), 3.94-4.00(2H, m), 4.04-4.10(2H, m), 4.87(1H, m), 5.85(1H, s), 6.81(2H, d, J=9.0Hz), 6.82(2H, d, J=8.9Hz), 7.10-7.21(4H, m).
IR (neat) : 3400, 3369, 2974, 2933, 1612, 1514cm^{-1}.
MS (ESI+) : m/z 369 (M+H).

Example 39

tert-Butyl 2-{4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (520mg, 72.2%) was prepared as a white powder from 4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 37 in a similar manner to that of Example 2.

1H NMR (DMSO-d6) : δ 1.31(6H, d, J=6.2Hz), 1.37(9H, s), 3.22-3.31(2H, m), 3.75(3H, s), 3.90-3.97(2H, m), 4.76(1H, m), 5.99(1H, s), 6.8

6-6.96(4H, m), 7.01(1H, t, J=5.6Hz), 7.09-7.15(4H, m).
MS (ESI+) : m/z 467 (M+H).

Example 40

2-{4-[3-Isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride

The title compound (557mg, quant.) was prepared as an amorphous from tert-butyl 2-{4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 39 in a similar manner to that of Example 3.

1H NMR (DMSO-d6) : δ 1.31(6H, d, J=6.1Hz), 3.12-3.28(2H, m), 3.76(3H, s), 4.00-4.18(2H, m), 4.76(1H, m), 6.01(1H, s), 6.92(2H, d, J=9.0Hz), 6.94(2H, d, J=8.7Hz), 7.10-7.19(4H, m), 8.06(2H, br-s).
MS (ESI+) : m/z 368 (M+H).

Example 41

N-(2-{4-[3-Isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (125mg, 79.8%) was prepared as a white powder from 2-{4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 40 in a similar manner to that of Example 4.

MP : 167.9-168.0℃.
1H NMR (DMSO-d6) : δ 1.31(6H, d, J=6.1Hz), 2.94(3H, s), 3.27-3.36(2H, m), 3.75(3H, s), 3.98-4.05(2H, m), 4.76(1H, m), 6.00(1H, s), 6.88-6.94(4H, m), 7.12(2H, d, J=9.0Hz), 7.14(2H, d, J=8.9Hz), 7.29(1H, t, J=5.8Hz).
IR (KBr) : 3132, 2979, 2939, 1612, 1556, 1518/cm^{-1}.

MS (ESI+) : m/z 446 (M+H).

Example 42

N-(2-{4-[3-Isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (76.3mg, 50.1%) was prepared as a white powder from 2-{4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 40 in a similar manner to that of Example 75 described later.

MP : 139-140℃.

1H NMR (DMSO-d6) : δ 1.31(6H, d, J=6.1Hz), 3.27-3.35(2H, m), 3.75(3H, s), 3.89-3.96(2H, m), 4.76(1H, m), 5.53(2H, s), 6.00(1H, s), 6.15(1H, t, J=5.7Hz), 6.90(2H, d, J=8.9Hz), 6.92(2H, d, J=9.0Hz), 7.08-7.15(4H, m).

IR (KBr) : 3388, 3350, 3332, 1658, 1612, 1579, 1562, 1554, 1518cm^{-1}.

MS (ESI+) : m/z 411 (M+H).

Example 43

5-[4-(Benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-3-ol

To a solution of 3-(4-benzyloxyphenyl)propiolic acid (1g) and 1-hydroxybenzotriazole hydrate (643mg) in N-methylpyrrolidone (10ml) was added WSCD·HCl (912mg) and the mixture was stirred at room temperature for 10min. In another flask, diisopropylethylamine (2.31g) was added to a suspension of 5-hydrazino-2-methoxypyridine dihydrochloride (1.26g) in N-methylpyrrolidone (4ml) and stirred at room temperature until all 5-hydrazino-2-methoxypyridine dihydrochloride was dissolved. Thus obtained hydrazine solution was added to the reaction flask and the mixture was stirred at room temperature for 1.5hrs.

The mixture was partitioned between ethyl acetate and 0.1M hydrochloric

acid, and the aqueous layer was reextracted with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in dichloroethane (15ml) and tetrakis(triphenylphosphine)palladium(0) (45.8mg) was added. The mixture was refluxed for 1hr and then concentrated in vacuo. The residue was crystallized from ethyl acetate to give the target compound (739mg, 49.9%) as a powder.

1H NMR (DMSO-d6) : δ 3.84(3H, s), 5.10(2H, s), 5.87(1H, s), 6.83(1H, d, J=8.7Hz), 7.00(2H, d, J=8.7Hz), 7.16(2H, d, J=8.7Hz), 7.29-7.48(5H, m), 7.54(1H, dd, J=2.6, 8.7Hz), 7.97(1H, d, J=2.6Hz), 10.13(1H, s).
MS (ESI+) : m/z (M+H).

Example 44

5-{5-[4-(Benzyloxy)phenyl]-3-isopropoxy-1H-pyrazol-1-yl}-2-methoxy pyridine

The title compound (1.33g, quant.) was prepared as a powder from 5-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-3-ol obtained by Example 43 in a similar manner to that of Example 36.

1H NMR ($CDCl_3$) : δ 1.40(6H, d, J=6.2Hz), 3.92(3H, s), 4.86(1H, m), 5.05(2H, s), 5.87(1H, s), 6.69(1H, d, J=8.8Hz), 6.91(2H, d, J=8.8Hz), 7.15(2H, d, J=8.8Hz), 7.35-7.43(5H, m), 7.51(1H, dd, J=2.7, 8.8Hz), 8.04(1H, d, J=2.7Hz).
MS (ESI+) : m/z 416 (M+H).

Example 45

4-[3-Isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol

The title compound (442.5mg, 54.9%) was prepared as a powder from 5-{5-[4-(benzyloxy)phenyl]-3-isopropoxy-1H-pyrazol-1-yl}-2-methoxypyridine obtained by Example 44 in a similar manner to that of Example 37.

1H NMR ($CDCl_3$) : δ 1.40(6H, d, J=6.2Hz), 3.91(3H, s), 4.84(1H, m), 5.80(1H, s), 5.87(1H, s), 6.71(1H, d, J=8.8Hz), 6.75(2H, d, J=8.6Hz), 7.08(2H, d, J=8.6Hz), 7.55(1H, dd, J=2.7, 8.8Hz), 8.00(1H, d, J=2.7Hz).

MS (ESI+) : m/z 326 (M+H).

Example 46

2-{4-[3-Isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanol

The title compound (94.6mg, 52.2%) was prepared as a white powder from 4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol obtained by Example 45 in a similar manner to that of Example 23.

MP : 74-75℃.

1H NMR ($CDCl_3$) : δ 1.40(6H, d, J=6.1Hz), 1.99(1H, t, J=6.1Hz), 3.91(3H, s), 3.94-4.00(2H, m), 4.05-4.11(2H, m), 4.86(1H, m), 5.88(1H, s), 6.69(1H, d, J=8.7Hz), 6.85(2H, d, J=8.7Hz), 7.15(2H, d, J=8.7Hz), 7.51(1H, dd, J=2.7, 8.7Hz), 8.03(1H, d, J=2.7Hz).

IR (KBr) : 3350, 1612, 1512, 1500cm^{-1}.

MS (ESI+) : m/z 370 (M+H).

Example 47

tert-Butyl 2-{4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (515.3mg, 87.6%) was prepared as a powder from 4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol obtained by Example 45 in a similar manner to that of Example 2.

1H NMR (DMSO-d6) : δ 1.32(6H, d, J=6.2Hz), 1.37(9H, s), 3.22-3.34(2H, m), 3.84(3H, s), 3.92(2H, t, J=5.7Hz), 4.77(1H, m), 6.06(1H, s), 6.84(1H, d, J=8.8Hz), 6.91(2H, d, J=8.8Hz), 7.01(1H, t, J=5.5Hz), 7.16(2H, d, J=8.8Hz), 7.58(1H, dd, J=2.7, 8.8Hz), 7.99(1H, d, J=2.7Hz).

Example 48

2-{4-[3-Isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanamine dihydrochloride

The title compound (531mg, quant.) was prepared as an amorphous from tert-butyl 2-{4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 47 in a similar manner to that of Example 3.

1H NMR (DMSO-d6) : δ 1.32(6H, d, J=6.1Hz), 3.15-3.24(2H, m), 3.84(3H, s), 4.19(2H, t, J=4.9Hz), 4.77(1H, m), 6.07(1H, s), 6.85(1H, d, J=8.8Hz), 6.97(2H, d, J=8.8Hz), 7.21(2H, d, J=8.8Hz), 7.60(1H, dd, J=2.7, 8.8Hz), 7.99(1H, d, J=2.7Hz), 8.22(2H, br-s).
MS (ESI+) : m/z 369 (M+H).

Example 49

N-(2-{4-[3-Isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (81.4mg, 60.2%) was prepared as a white powder from 2-{4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanamine dihydrochloride obtained by Example 48 in a s

imilar manner to that of Example 75 described later.

MP : 120℃.

1H NMR (DMSO-d6) : δ 1.32(6H, d, J=6.2Hz), 3.27-3.36(2H, m), 3.84(3H, s), 3.94(2H, t, J=5.5Hz), 4.77(1H, m), 5.52(2H, s), 6.06(1H, s), 6.15(1H, t, J=5.6Hz), 6.84(1H, d, J=8.8Hz), 6.93(2H, d, J=8.8Hz), 7.17(2H, d, J=8.8Hz), 7.58(1H, dd, J=2.7, 8.8Hz), 7.99(1H, d, J=2.7Hz).

IR (KBr) : 3400, 3330, 1658, 1612, 1514, 1500cm^{-1}.

MS (ESI+) : m/z 412 (M+H).

Example 50

N-(2-{4-[3-Isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (94.4mg, 58.4%) was prepared from 2-{4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanamine dihydrochloride obtained by Example 48 in a similar manner to that of Example 4.

MP : 121.0-121.6℃.

1H NMR (DMSO-d6) : δ 1.32(6H, d, J=6.1Hz), 2.94(3H, s), 3.29-3.34(2H, m), 3.84(3H, s), 4.00-4.06(2H, m), 4.77(1H, m), 6.06(1H, s), 6.85(1H, d, J=8.7Hz), 6.94(2H, d, J=8.8Hz), 7.18(2H, d, J=8.8Hz), 7.28(1H, br-s), 7.58(1H, dd, J=2.7, 8.7Hz), 7.99(1H, d, J=2.7Hz).

IR (KBr) : 3242, 1612, 1514, 1502cm^{-1}.

MS (ESI+) : m/z 447 (M+H).

Example 51

2-{4-[1-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl methanesulfonate

To a solution of 2-{4-[1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanol (2.72g) and triethylamine (1.55ml) in dichloromethane (30ml) was added dropwise methanesulfonyl chloride (0.86ml) under ice-cooling. The reaction mixture was allowed to warm to room temperature and stirred for 1hr.

The reaction mixture was quenched with water. The organic layer was separated and washed with 1N hydrochloric acid and water, dried over sodium sulfate, filtered and evaporated under reduced pressure to give the target compound (3.25g, 98.5%).

1 HNMR ($CDCl_3$) : δ 2.929(3H, s), 3.072(2H, t, J=6.7Hz), 4.427(2H, t, J=6.7Hz), 6.739(1H,), 7.175(2H, d, J=8.4Hz), 7.234(2H, d, J=8.4 Hz), 7.253(2H, d, J=8.9Hz), 7.344(2H, d, J=8.8Hz).
MS (ESI+): m/z 467 (M+Na).

Example 52

2-(2-{4-[1-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione

A mixture of 2-{4-[1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl methanesulfonate obtained by Example 51 (3.2g) and Potassium phthalimide (1.6g) was stirred at 80℃ for 5hrs.

After cooling, the mixture was diluted with water and ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate (twice). The combined organic layer was washed with water (twice) and brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure to give the target compound (1.55g, 43.5%) as a powder.

1H NMR ($CDCl_3$) : δ 1.59(3H, s), 3.02(2H, t, J=7.3Hz), 3.94(2H, t, J=7.3Hz), 6.71(1H, s), 7.11(2H, d, J=8.2Hz), 7.21(2H, d, J=7.6Hz), 7.24(2H, d, J=8.4Hz), 7.32(2H, d, J=8.9Hz), 7.70-7.86(4H, m).
MS (ESI+) : m/z 518 (M+Na).

Example 53

2-{4-[1-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanamine

A mixture of 2-(2-{4-[1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 52 (1.5g) and hydrazine (2.93ml) in acetonitrile (30ml) was stirred at 60℃ for 5hrs.

After cooling, the mixture was filtered and washed with acetonitrile. The filtrate was evaporated under reduced pressure to give the target compound (1.1g, quant.) as an oil.

1H NMR ($CDCl_3$): δ 3.09(2H, dd, J=5.6Hz, 9.3Hz), 3.24(2H, dd, J=5.6Hz, 8.6Hz), 5.47(2H, s), 6.69(1H, s), 7.12(1H, d, J=8.2Hz), 7.21(1H, d, J=8.2Hz), 7.22(1H, d, J=8.9Hz), 7.32(1H, d, J=8.9Hz).
MS (ESI+) : m/z 366 (M+1).

Example 54

N-(2-{4-[1-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl)methanesulfonamide

To a solution of 2-{4-[1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanamine obtained by Example 53 (400mg) and triethylamine (0.46ml) in dichloromethane (20ml) was added dropwise methanesulfonyl chloride (0.25ml) at room temperature.

After stirring for 1hr, the reaction mixture was quenched with 1N hydrochloric acid. The aqueous layer was separated and extracted twice with chloroform. The combined organic layer was washed with 1N hydrochloric acid, sodium hydrogencarbonate solution, water, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel

(chloroform/methanol=4:1) to give the target compound (166mg, 34.2%) as an oil.

1H NMR ($CDCl_3$): δ 2.899(3H, s), 2.904(2H, t, J=6.9Hz), 3.417(2H, dt, J=6.7 ,6.8Hz), 4.272(1H, t, J=6.1Hz), 6.737(1H, s), 7.178(2H, d, J =8.4Hz), 7.21(2H, d, J=8.4Hz), 7.255(2H, d, J=8.8Hz), 7.35(2H, d, J =8.8Hz).

IR (Film) : 3346, 1657, 1597, 1552, 1496, 1471, 1236, 1163, 1136, 10 92, 978, 835, 756 cm^{-1}.

MS (ESI-) : 442 (M-1).

Example 55

N-(2-{4-[1-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]ph enyl}ethyl)urea

To a solution of 2-{4-[1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanamine obtained by Example 53 (300mg) an d triethylamine (0.57ml) in dichloromethane (10ml) was added dropwi se trimethylsilyl isocyanate (0.555ml) at room temperature.

After stirring overnight, the reaction mixture was quenched with 1N hydrochloric acid. Aqueous layer was separated and extracted twice with chloroform. The combined organic layer was washed with 1N hydrochloric acid, sodium hydrogencarbonate solution, water, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (chloroform/methanol=4:1) to give the target compound (205mg, 61.1%) as an amorphous.

1H NMR ($CDCl_3$): δ 2.83(2H, t, J=7Hz), 3.43(2H, dt, J=6.6Hz, 6.8Hz), 4.41(2H, s), 4.61(1H, t, J=5.4Hz), 6.72(1H, s), 7.16(4H, s), 7.25 (2H, d, J=8.8Hz), 7.34(2H, d, J=8.8Hz).

IR (Film): 3346, 1657, 1597, 1552, 1496, 1471, 1448, 1375, 1271, 12

36, 1163, 1136, 1092, 978, 835, 756 cm^{-1}.
MS (ESI+) : m/z 431 (M+Na).

Example 56

4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzonitrile

A mixture of 4-(4,4,4-trifluoro-3-oxobutanoyl)benzonitrile (1.0g), 4-methoxyphenylhydrazine hydrochloride (760mg), and sodium acetate (357mg) in acetic acid (10ml) was stirred at 80℃ for 4hrs.

After cooling, the reaction mixture was poured into water and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate. Combined organic layers were washed with saturated sodium hydrogencarbonate solution (twice), water and brine, dried over sodium sulfate, and evaporated under reduced pressure to give crude product. The crude product was column chromatographed on silica gel (50ml, n-hexane:ethyl acetate=5:1-4:1) and triturate with petroleum ether to give the target compound (553mg, 38.8%).

1H NMR ($CDCl_3$) : δ 3.84(3H, s), 6.82(1H, s), 6.9(2H, d, J=9Hz), 7.2(2H, d, J=9Hz), 7.33(2H, d, J=8.6Hz), 7.62(2H, d, J=8.6Hz).
IR (Film) : 2229, 1610, 1512, 1468, 1240, 1161, 1132, 839 cm^{-1}.
MS (ESI+) : m/z 366 (M+Na).

Example 57

4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzylamine hydrochloride

A mixture of 4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzonitrile obtained by Example 56 (430mg), Pd/C (100mg) and 1N hydrochloric acid (1.3ml) in methanol (43ml) was stirred under Hydrogen atmosphere

for 5hrs.

The reaction mixture was filtered with paper filter, and filtrate was evaporated. After dissolving in methanol, the solution was filtered with membrane filter. The filtrate was evaporated to give the target compound (450mg, 93.6%) as crystals.

1H NMR ($CDCl_3$) : δ 3.79(3H, s), 4.04(2H, br-s), 6.69(1H, s), 6.85(2H, d, J=8.9Hz), 7.13(2H, d, J=8.9Hz), 7.24(2H, d, J=9Hz), 7.42(2H, d, J=9Hz).

IR (Film) : 2964, 1512, 1468, 1238, 1161, 1130, 976, 837cm^{-1}.

MS (ESI+) : m/z 331 (M-Cl-NH_3).

Example 58

N-{4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

To a solution of 4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzylamine hydrochloride obtained by Example 57 (100 mg) and triethylamine (0.073ml) in chloroform (10ml) was added drop wise methanesulfonyl chloride (0.04ml) at room temperature.

After stirring for 1hr, the reaction mixture was partitioned between chloroform and water. The organic layer was washed with water, sodium bicarbonate solution, brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure to give the target compound (90mg, 81.2%) as an oil.

1H NMR ($CDCl_3$) : δ 2.93(3H, s), 3.82(3H, s), 4.32(2H, d, J=6.2Hz), 4.71(1H, t, J=6.2Hz), 6.73(1H, s), 6.86(2H, d, J=9Hz), 7.21(2H, d, J=9Hz), 7.21(2H, d, J=8.3Hz), 7.31(2H, d, J=8.3Hz).

IR (Film) : 3282, 1514, 1321, 1240, 1151, 974, 837cm^{-1}.

MASS (ESI+) : m/z 426 (M+1).

Example 59

4-[3-(Difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzonitrile

The title compound (4.5g, 20.6%) was prepared from 4-(4,4-difluoro-3-oxobutanoyl)benzonitrile in a similar manner to that of Example 56.

1H NMR ($CDCl_3$) : δ 3.84(3H, s), 6.77(1H, t, J=54.9Hz), 6.8(1H, s), 6.9(2H, d, J=9Hz), 7.19(2H, d, J=9Hz), 7.33(2H, d, J=8.6Hz), 7.61 (2H, d, J=8.6Hz).
MS (ESI+) : m/z 348 (M+Na).

Example 60

1-{4-[3-(Difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}methanamine hydrochloride

The title compound (510mg, 45.4%) was prepared from 4-[3-(Difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzonitrile obtained by Example 59 in a similar manner to that of Example 57.

1H NMR (DMSO-d6) : δ 3.35(3H, s), 3.79(2H, s), 7.1(1H, t, J=54.5Hz), 6.95(1H, s), 6.99(2H, d, J=8.8Hz), 7.26(2H, d, J=8.8Hz), 7.3(2H, d, J=8.3Hz), 7.49(2H, d, J=8.3Hz).
MS (ESI-): m/z 365 (M-HCl).

Example 61

N-{4-[3-(Difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

The title compound (146mg, 65.5%) was prepared from 1-{4-[3-(difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}methanami

ne hydrochloride obtained by Example 60 in a similar manner to that of Example 58.

1H NMR ($CDCl_3$) : δ 2.90(3H, s), 3.82(3H, s), 4.31(2H, d, J=6.2Hz), 4.73(1H, t, J=6.2Hz), 6.72(1H, s), 6.77(1H, t, J=55Hz), 6.86(2H, d, J=9Hz), 7.19(2H, d, J=9Hz), 7.22(2H, d, J=8.4Hz), 7.30(2H, d, J=8.4Hz).

IR (film) : 3143, 1518, 1508, 1452, 1325, 1244, 1151, 1074, 1022, 972, 843, 793 cm^{-1}.

MS (ESI-) : m/z 406 (M-1).

Example 62

N-{4-[3-(Difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}urea

To a solution of 1-{4-[3-(difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}methanamine hydrochloride obtained by Example 60 (100mg) in dichloromethane (1ml) was added dropwise triethylamine (0.163ml) and trimethylsilyl isocyanate (0.11ml) at room temperature.

The mixture was stirred at room temperature overnight and quenched by adding saturated sodium hydrogencarbonate solution (0.5ml). The mixture was filtered by Chemelute. The elution was evaporated and purified by preparative thin layer chromatography (0.5mm, 10%methanol/chloroform) to give solid. The solid was added ethyl acetate and n-hexane, and the precipitate was collected by filtration to give the target compound(160mg, 62.9%).

1H NMR ($CDCl_3$) : δ 3.82(3H, s), 4.35(2H, d, J=6Hz), 4.46(2H, br-s), 4.99(1H, t, J=6Hz), 6.69(1H, s), 6.76(1H, t, J=55.1Hz), 6.86(2H, d, J=9Hz), 7.14-7.21(6H, m).

MS (ESI+) : m/z 395 (M+Na).

IR (film) : 1657, 1608, 1593, 1550, 15120, 1510, 1467, 1338, 1252, 1171, 1088, 1030, 837, 796cm^{-1}.

Example 63

4-[1-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzonitrile

The title compound (942mg, 86.8%) was prepared from 4-(4,4,4-trifluoro-3-oxobutanoyl)benzonitrile in a similar manner to that of Example 56.

1H NMR ($CDCl_3$) : δ 2.39(3H, s), 6.82(1H, s), 7.15(2H, d, J=8.9Hz), 7.21(2H, d, J=8.8Hz), 7.33(2H, d, J=8.3Hz), 7.62(2H, d, J=8.3Hz).
MS (ESI+): m/z 328 (M+1).

Example 64

1-{4-[1-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}methanamine hydrochloride

The title compound (414mg, 92.1%) was prepared from 4-[1-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzonitrile obtained by Example 63 in a similar manner to that of Example 57.

1H NMR (DMSO-d6) : δ 2.35(3H, d, J=4.2Hz), 3.35(2H, s), 7.17(1H, s), 7.17-7.29(4H, m), 7.32(2H, d, J=8.1Hz), 7.51(2H, d, J=8.2Hz).
MS (ESI+): m/z 332 (M+1).

Example 65

N-{4-[1-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}urea

The title compound (81mg, 31.8%) was prepared from 1-{4-[1-(4-m

ethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}methanamin e hydrochloride obtained by Example 64 in a similar manner to that o f Example 62.

1H NMR ($CDCl_3$) : δ 2.36(3H, s), 4.35(2H, d, J=5.9Hz), 4.50(2H, br-s), 5.02(1H, t, J=5.5Hz), 6.71(1H, s), 7.16(4H, s), 7.20(4H, d, J=5.7Hz).

IR (film) : 3344, 1658, 1600, 1552, 1518, 1236, 1159, 1134cm^{-1}.

MS (ESI+) : m/z 397 (M+Na).

Example 66

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzonit rile

The title compound (1.05g, 73.8%) was prepared from 4-methyl-1-(4,4,4-trifluoro-3-oxobutanoyl)benzene in a similar manner to that of Example 69 described later.

MP : 125.0-125.5℃.

1H NMR (CDCl3) : δ 2.39(3H, s), 6.74(1H, s), 7.10(2H, d, J=8.1Hz), 7.19(2H, d, J=8.2Hz), 7.45(2H, d, J=8.7Hz), 7.65(2H, d, J=8.7Hz).

MASS (ESI+) : m/z 350 (M+Na).

Example 67

1-{4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]pheny l}methanamine hydrochloride

The title compound (830mg, 92.3%) was prepared from 4-[5-(4-met hylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzonitrile obtain ed by Example 66 in a similar manner to that of Example 70 described later.

1H NMR (DMSO-d6) : δ 2.30(3H, d, J=2.3Hz), 4.07(2H, s), 7.15(1H, s), 7.15(2H, d, J=9.0Hz), 7.21(2H, d, J=8.9Hz), 7.39(2H, d, J=8.5Hz), 7.58(2H, d, J=8.5Hz).

MS (ESI+) : m/z 332 (M+1).

Example 68

N-{4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzyl}urea

The title compound (65mg, 31.9%) was prepared from 1-{4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}methanamine hydrochloride obtained by Example 67 in a similar manner to that of Example 72 described later.

1H NMR ($CDCl_3$) : δ 2.34(3H, s), 4.34(2H, d, J=5.8Hz), 4.56(2H, br-s), 5.23(1H, t, J=5.8Hz), 6.71(1H, s), 7.07(2H, d, J=8.7Hz), 7.13(2H, d, J=8.7Hz), 7.24(4H, s).

IR (film) : 3344, 1658, 1604, 1552, 1234, 1159, 1134cm^{-1}.

MS (ESI+) : 397 (M+Na).

Example 69

4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzonitrile

A mixture of 4-methoxy-1-(4,4,4-trifluoro-3-oxobutanoyl)benzene (1.0g), 4-methoxyphenylhydrazine hydrochloride (758mg) and sodium acetate (367mg) in acetic acid (5ml) was stirred overnight at room temperature.

After then, the reaction mixture was poured into water and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate. Combined organic layers were washed with water, saturated sodium hydrogencarbonate (twice) and brine, dried over sodium sulfate, and

evaporated under reduced pressure to give crude product. The crude product was column chromatographed on silica gel (50ml, n-hexane:ethyl acetate=10:1-5:1) to give the target compound (930mg, 66.7%).

1HNMR($CDCl_3$) : δ 3.84(3H, s), 6.72(1H, s), 6.9(2H, d, J=8.9Hz), 7.14(2H, d, J=8.9Hz), 7.46(2H, d, J=8.7Hz), 7.66(2H, d, J=8.7Hz).
MS (ESI+) : m/z 366 (M+Na).

Example 70

4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzylamine hydrochloride

A mixture of 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzonitrile obtained by Example 69 (400mg) and 50% wet pd/C (400mg) in ethanol (10ml) and 1N hydrochloric acid (1.2ml) was stirred under hydrogen atmosphere for 8hrs.

The mixture was filtered and filtrate was evaporated under reduced pressure. The residue was washed with isopropylether to give the target compound (400mg, 89.4%) as a powder.

1H NMR ($CDCl_3$) : δ 3.36(s, 3H), 3.76(d, J=2.4, 2Hz), 6.94(d, J=8.7, 2Hz), 7.12(s, 1H), 7.23(d, J=8.7, 2Hz), 7.39(d, J=8.4, 2Hz), 7.59 (d, J=8.4, 2Hz).
MS (ESI+) : m/z 348 (M+1).

Example 71

N-{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzyl}methanesulfonamide

To a solution of 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzylamine hydrochloride obtained by Example 70 (150 mg) and triethylamine (0.1ml) in dichloromethane (10ml) was added d

ropwise methanesulfonyl chloride (0.06ml) under ice cooling.

After stirring for 1hr, the reaction mixture was quenched and partitioned between chloroform and water. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water, 1N hydrochloric acid, saturated sodium hydrogencarbonate solution and brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was chromatographed by high performanced thin layer chromatography to give the target compound (67mg, 40.3%).

1H NMR ($CDCl_3$) : δ 2.91(3H, s), 3.82(s, 3H), 4.35(2H, d, J=6.1Hz), 4.69(1H, t, J=6.1Hz), 6.69(1H, s), 6.84(2H, d, J=8.6Hz), 7.13(2H, d, J=8.6Hz), 7.32(2H, d, J=9Hz), 7.37(2H, d, J=9Hz).

IR (film) : 3207, 1479, 1456, 1323, 1252, 1234, 1146, 1122, 984, 968, 962, 841, 802cm^{-1}.

MS (ESI+) : m/z 448 (M+Na).

Example 72

N-{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzyl}urea

To a solution of 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzylamine hydrochloride obtained by Example 70 (150 mg) in water (8ml) and ethanol (4ml) was added sodium cyanate (100mg) under ice cooling.

After stirring for 3hrs, the reaction mixture was partitioned between chloroform and water. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water and brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was chromatographed by high performanced thin layer chromatography to give the target compound (105mg, 69%).

1H NMR ($CDCl_3$) : δ 3.80(3H, s), 4.35(2H, d, J=5.9Hz), 4.53(2H, br-s), 5.171(1H, t, J=5.7Hz), 6.68(1H, s), 6.84(2H, d, J=8.7Hz), 7.12 (2H, d, J=8.7Hz), 7.25(4H, s).

MS (ESI+) : m/z 413 (M+Na).

Example 73

tert-Butyl 2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

To solution of 4-[1-(4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazol-5-yl]phenol (500g) in N,N-dimethylformamide (1.5L) was added sodium hydride (dispersion in mineral oil, 77.8g) over 25min under ice cooling. The mixture was warmed to room temperature over 10min and then stirred at room temperature for 30min. A solution of 2-tert-butoxycabonylaminoethyl bromide (469g) in N,N-dimethylformamide (300ml) was added to the mixture over 10min at 25-28℃, and the whole mixture was stirred at 60℃ for 6hrs.

After allowed to stand overnight, the mixture was poured into a mixture of water (4.5L) and toluene (3L). The organic layer was separated, and the aqueous layer was extracted with toluene (1.5L). The combined organic layers were washed with water (1.5L×3) and brine (1.5L), dried over magnesium sulfate, filtered and evaporated to give the oil (1.02kg). The oil was purified with silica gel column chromatography [5L, n-hexane (10L), 50% ethyl acetate/n-hexane (30L)] to give the target compound (680g, 95%) as a pale yellow oil.

MP : 104.7-105.1℃.

1HNMR ($CDCl_3$) : δ 1.45(3H, s), 3.53(2H, dt, J=4Hz), 3.82(3H, s), 4.01(2H, t, J=4Hz), 6.67(1H, s), 6.83(2H, d, J=8Hz), 6.87(2H, d, J=8Hz), 7.13(2H, d, J=8Hz), 7.23(2H, d, J=8Hz).

Example 74

2-{4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride

To a solution of hydrogen chloride in ethyl acetate (4N, 1.0L) was added powdered tert-Butyl 2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 73 (500g) at 5℃ over 20min.

After stirring at the same temperature for 30min and then at room temperature for 1hr, the mixture was evaporated to give oil (543.12g). The oil was dissolved in toluene (1.5L). And then, n-hexane (200ml) and the target compound (as seeds for crystallization) were added to the solution. The mixture was stirred at room temperature overnight. And the precipitate was filtered, washed with toluene (500ml×2) and isopropylether (650ml), and dried to give the target compound (420.5g, 97%) as a white powder.

MP : 166.8-168.0℃.

1HNMR (DMSO-d6) : δ 3.185(2H, t, J=5Hz), 3.8(3H, s), 4.215(2H, t, J=5Hz), 6.96-7.05(4H, m), 7.1(1H, s), 7.22-7.33(4H, m).

Example 75

N-(2-{4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

2-{4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 74 (400g) and sodium acetate (159g) was dissolved in a mixture of N,N-dimethylformamide (1.4L) and water (0.52L) at 50℃. A solution of potassium cyanate (157g) in water (520ml) was added dropwise to the solution over 15min at 38-40℃. The whole solution was stirred at 50℃ for 2hrs.

The solution was filtered and washed with N,N-dimethylformamide

(0.68L) at the same temperature. The filtrate was cooled to room temperature, and then water (0.4L) and the target compound (A04 type crystal) was added as seeds for crystallization to the filtrate, and the mixture was stirred at room temperature for 30min. Then water (2.76L) was added dropwise to the mixture over 30min, and the mixture was stirred at room temperature for 30min. The precipitate was filtered, washed with water (0.8L×3), and dried under reduced pressure at 45℃ overnight to give the target compound (A04 type crystals, 442.01g) as a white powder.

1HNMR ($CDCl_3$) : δ 3.555(2H, dt, J=5, 6Hz), 3.81(3H, s), 3.995(2H, t, J=5Hz), 4.67(2H, s), 5.37(1H, t, J=6Hz), 6.66(1H, br-s), 6.79(2H, d, J=8Hz), 6.845(2H, d, J=6Hz), 7.11(2H, d, J=8Hz), 7.19(2H, d, J=8Hz).
1HNMR (DMSO-d6) : δ 3.28-3.36(2H, m), 3.79(3H, s), 3.945(2H, t, J=5Hz), 5.54(2H, br-s), 6.165(1H, t, J=5Hz), 6.92-7.08(5H, m), 7.2(2H, d, J=8Hz), 7.28(2H, d, J=8Hz).

Example 76

2-Hydroxy-N-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}acetamide

To a solution of 4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzylamine hydrochloride obtained by Example 57 (46.5mg) in dichloromethane (1.5ml) was added diisopropylethylamine (135μL) and acetoxyacetylchloride (41.6μL) at 0℃.

After stirring at room temperature for 3hrs, the mixture was quenched with water. The whole mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to give oil (67mg). The oil was dissolved in methanol (1.5ml). Potassium carbonate (55mg) was added to the solution. After stirring at room temperature for 3hrs, the mixture was filtered and evaporated to give oil which was purified with preparative thin

layer chromatography (0.5mm×2, 10% methanol/chloroform) to give colorless oil (42.5mg). The oil was crystallized from a mixture of ethyl acetate, diisopropylether, and n-hexane with stirring at room temperature. The precipitate was filtered and dried to give the target compound (33.9mg, 64.8%) as a white powder.

1HNMR ($CDCl_3$) : δ 2.32(1H, t, J=5.2Hz), 3.83(3H, s), 4.20(2H, d, J=5.2Hz), 4.51(2H, d, J=6.1Hz), 6.72(1H, s), 6.87(2H, d, J=8.9Hz), 7.16-7.24(6H, m).

MS (ESI+) : 428.2(M+Na).

Example 77

2-Hydroxy-N-(2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl)ethanesulfonamide

To a solution of 2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanamine hydrochloride and triethylamine in chloroform was added methanesulfonyl chloride at room temperature.

After stirring for 1hr, the reaction mixture was poured into water and chloroform. The aqueous layer was separated and extracted with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel and crystallized to give the target compound (27.7mg, 23.5%).

1HNMR ($CDCl_3$) : δ 2.78-2.91(2H, m), 3.16(2H, t, J=5.1Hz), 3.32-3.43(2H, m), 3.82(3H, s), 3.96(2H, t, J=5.1Hz), 4.65(1H, t, J=6.2Hz), 6.72(1H, s), 6.87(2H, d, J=9.0Hz), 7.12-7.27(6H, m).

MS(LC, ESI+), 470.21(MH+), 511.17(MHMeCN).

Example 78-1

tert-Butyl 2-(4-acetylphenoxy)ethylcarbamate

To a solution of 4-hydroxyacetophenone (10g) and 2-tert-butoxycarbonylaminoethylbromide (24.7g) in N,N-dimethylformamide (50 ml) was added potassium iodide (12.2g) and potassium carbonate (15.2g).

After stirring at 50℃ overnight, the mixture was quenched with water and extracted with ethyl acetate (3 times). The combined organic layers were washed with 1N sodium hydroxide aqueous solution (2 times) and brine, dried over magnesium sulfate, and evaporated to give oil. The oil was purified with silica gel column chromatography [500ml, 20% ethyl acetate/n-hexane (1000ml), 30% ethyl acetate/n-hexane (1000ml)] to give the target compound (19.89g, 96.9%) as a white solid.

1HNMR($CDCl_3$) : δ 1.46(9H, s), 2.56(3H, s), 3.52-3.60(2H, m), 4.09(2H, t, J=5.1Hz), 6.93(2H, d, J=8.9Hz), 7.93(2H, d, J=8.9Hz).
MS (ESI+) : 280.09(MH+).

Example 78-2

tert-Butyl 2-[4-(4,4,4-trifluoro-3-oxobutanoyl)phenoxy]ethylcarbamate

A mixture of tert-butyl 2-(4-acetylphenoxy)ethylcarbamate obtained by Example 78-1 (15g), trifluoroacetic acid (8.95ml), and sodium ethoxide (8.77g) in ethanol (45ml) was stirred at 70℃ for 2.5hrs.

The mixture was poured into a mixture of aqueous hydrogen chloride solution (1N) and ethyl acetate. The whole mixture was extracted with ethyl acetate (2 times). The organic layer was separated, washed with saturated sodium hydrogencarbonate and brine, dried over magnesium sulfate, and evaporated to give oil (25g). The oil was purified with silica gel column chromatography [500ml, 30% ethyl acetate/n-hexane (1000ml)] to give oil. The oil was dissolved in ethyl acetate (5ml)

under heating by water bath. n-Hexane (100ml) was added to the solution, and the solution was cooled to room temperature over 30min under stirring. And n-hexane (100ml) was added to the mixture. The precipitate was filtered and dried to give the target compound (15.956g, 79.2%) as an orange powder.

1HNMR ($CDCl_3$) : δ 3.40-3.70(2H, m), 4.00-4.20(2H, m), 5.00(1H, br-s), 6.50(1H, s), 6.98(2H, d, J=8.6Hz), 7.93(2H, d, J=8.6Hz).

Example 78-3

tert-Butyl 2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

To a suspension of 4-methoxyaniline (100mg) in a mixture of acetic acid (2ml) and concentrated hydrogen chloride (0.4ml) was added dropwise a solution of sodium nitrite (61.6mg) in water (0.1ml) over 5min at 3℃, and the mixture was stirred at 3℃ for 1hr. To the mixture was added dropwise a solution of tin chloride (641mg) in concentrated hydrogen chloride (0.3ml) at 0℃ over 10min, and then the mixture was stirred at 0℃ for 1hr. Acetic acid (5ml) was added dropwise to the mixture at between -20 and -10℃ over 2min, and then the mixture was quenched with a solution of sodium hydroxide (336mg) in water (2.24ml) at -10℃ over 2min and warmed to room temperature to give a solution containing 4-methoxyphenylhydrazine hydrochloride.

A solution of tert-butyl 2-[4-(4,4,4-trifluoro-3-oxobutanoyl)phenoxy]ethylcarbamate obtained by Example 78-2 (305mg) was added to the former solution at -10℃, and then the mixture was stirred at room temperature for 3hrs. The mixture was poured into a mixture of saturated sodium hydrogen carbonate aqueous solution (150ml) and ethyl acetate (100ml), and adjusted pH to basic by sodium hydrogencarbonate powder.

The organic layer was separated and the aqueous layer was extracted

with ethyl acetate (50ml×2). The combined organic layers were washed with saturated sodium hydrogen carbonate aqueous solution and brine, dried over magnesium sulfate, filtered, and evaporated to give oil (450 mg). The oil was purified with silica gel column chromatography [35 ml, 15% ethyl acetate/n-hexane (800ml)] to give an oil. (343.2mg, 88.5%). The oil was dissolved in isopropylether (2ml), and then n-hexane (6ml) was added to the solution. The whole mixture was stirred at room temperature for 1hr. And then the precipitate was filtered, washed with n-hexane (10ml), and dried under reduced pressure for 2hrs to give the target compound (280.6 mg, 72.4%) as a white powder.

1HNMR ($CDCl_3$) data was identical to authentic sample.

1HNMR ($CDCl_3$) : δ 1.45(3H, s), 3.53(2H, dt, J=4.4Hz), 3.82(3H, s), 4.01(2H, t, J=4Hz), 6.67(1H, s), 6.83(2H, d, J=8Hz), 6.87(2H, d, J=8Hz), 7.13(2H, d, J=8Hz), 7.23(2H, d, J=8Hz).

Example 79-1

1-[4-(Benzyloxy)phenyl]hydrazine hydrochloride

To the suspension of 4-benzyloxyaniline (10g) in concentrated hydrogen chloride (100ml) was added dropwise a solution of sodium nitrite (3.2g) in water (10ml) over 10min at between -15 and -10℃, and then the mixture was stirred at 3℃ for 1hr. To the mixture was added dropwise a solution of tin chloride (33.5g) in concentrated hydrogen chloride (80ml) at between -20 and -10℃ over 30min, and then the mixture stirred at 0℃ for 1hr.

After cooling to -20℃, the precipitate was filtered, washed with water (25ml), ethanol (25ml) and ether (50ml), and dried to give the target compound (10.637g, 100%) as a pale brown powder.

NMR(DMSO-d6) : δ 5.05(2H, s), 6.93-7.03(4H, m), 7.46-7.28(4H, m).

Example 79-2

2-{4-[1-(4-Benzyloxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxyl}ethanamine hydrochloride

The title compound (12.9g, 87.5%) was prepared from 1-[4-(benzyloxy)phenyl]hydrazine hydrochloride obtained by Example 79-1 and tert-butyl 2-[4-(4,4,4-trifluoro-3-oxobutanoyl)phenoxy]ethylcarbamate obtained by Example 78-2 in a similar manner to that of Example 78-3.

1HNMR (DMSO-d6) : δ 3.10-3.30(2H, m), 4.19(2H, t, J=6.3Hz), 5.14(2H, s), 6.98(2H, d, J=8.7Hz), 7.09(1H, s), 7.09(2H, d, J=8.9Hz), 7.49-7.22(9H, m).

Example 80

N-(2-{4-[1-[4-(Benzyloxy)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (10.57g, 84.3%) was prepared from 2-{4-[1-(4-benzyloxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxyl}ethanamine hydrochloride obtained by Example 79-2 in a similar manner to that of Example 75.

1HNMR ($CDCl_3$) : δ 3.57(2H, td, J=5.7, 5.0Hz), 4.01(2H, t, J=5.0Hz), 4.57(1H, br-s), 5.06(2H, s), 5.20(1H, t, J=5.7Hz), 6.66(1H, s), 6.80(2H, d, J=8.7Hz), 6.93(2H, d, J=9.0Hz), 7.12(2H, d, J=8.7Hz), 7.21(2H, d, J=9.0Hz), 7.35-7.42(5H, m).

Example 81

N-(2-{4-[1-(4-Hydroxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

To a solution of N-(2-{4-[1-[4-(benzyloxy)phenyl]-3-(trifluoro methyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea obtained by Example 80 (10.33g) in methanol (100ml) was added palladium on carbon (10% wet, 2g), and the mixture was stirred vigorously at room temperature under hydrogen atmosphere for 3hrs. The whole mixture was filtered and evaporated to give oil (8.23g). The oil was purified with silica gel column chromatography [250ml, 3% methanol/chloroform (500ml), 5% methanol/chloroform (500ml), and 10% methanol/chloroform (500ml)] to give the target compound (8.07g, 95.4%) as an oil.

1HNMR (DMSO-d6) : δ 3.28-3.33(2H, m), 3.94(2H, t, J=5.5Hz), 5.52(2H, br-s), 6.14(1H, br-t, J=5.7Hz), 6.80(2H, d, J=8.7Hz), 6.93(2H, d, J=8.9Hz), 7.05(1H, s), 7.14(2H, d, J=8.7Hz), 7.19(2H, d, J=8.9Hz).
MS (ESI+) : 407.10(MH+).

Example 82

4-[5-(4-{2-[(Aminocarbonyl)amino]ethoxy}phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl acetate

To a mixture of N-(2-{4-[1-(4-hydroxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea obtained by Example 81 (148.5mg) in dichloromethane (1.5ml) was added pyridine (163μL) and acetic anhydride (45μL), and the mixture was stirred at room temperature for 1hr and stirred under reflux for 3hrs.

After evaporation, the mixture was purified with preparative thin layer chromatography (1.0mm, 10% methanol/chloroform) to give oil. The oil was crystallized from a mixture of dichloromethane and isopropylether at room temperature to give the target compound (138.6mg, 84.6%) as a white powder.

1HNMR ($CDCl_3$) : δ 2.30(3H, s), 3.59(2H, td, J=5.5, 4.9Hz), 4.04(2H, t, J=4.9Hz), 4.51(2H, br-s), 5.22(1H, br-t, J=5.5Hz), 6.69(1H, s),

6.84(2H, d, J=8.7Hz), 7.10(2H, d, J=8.8Hz), 7.14(2H, d, J=8.7Hz), 7.31(2H, d, J=8.9Hz).

MS(LC, ESI+) : 449.24(MH^+), (ESI-) 492.5($M-H+HCO_2^-$).

Example 83-1

1-(1,3-Benzodioxol-5-yl)hydrazine hydrochloride

The title compound (1.811g, quant.) was prepared from 3,4-(methylenedioxy)aniline in a similar manner to that of Example 79-1.

1HNMR (DMSO-d6) : δ 5.94(2H, s), 6.53(1H, dd, J=2.2 8.2Hz), 6.80(1H, s), 6.83(1H, d, J=8.2Hz).

MS(LS, ESI+): 153.9(MH+) 193.99($MH+CH_3CN$).

Example 83-2

tert-Butyl 2-{4-[1-(1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (371.3mg, 56.7%) was prepared from tert-butyl 2-[4-(4,4,4-trifluoro-3-oxobutanoyl)phenoxy]ethylcarbamate obtained by Example 78-2 and 1-(1,3-benzodioxol-5-yl)hydrazine hydrochloride obtained by Example 83-1 in a similar manner to that of Example 78-3.

NMR ($CDCl_3$) MA12.048 : δ 1.75(9H, s), 3.45-3.60(2H, m), 4.02(2H, t, J=5.1Hz), 6.02(2H, s), 6.66-6.88(1H, m), 7.16(2H, d, J=8.8Hz).

MS(LC, ESI+) : 492.22 (MH+), 533.26 (MHMeCN+).

Example 84

2-{4-[1-(1,3-Benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethanamine

The title compound (181.2mg, 61.5%) was prepared from tert-butyl 2-{4-[1-(1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 83-2 in a similar manner to that of Example 74.

1HNMR ($CDCl_3$) : δ 1.75(9H, s), 3.45-3.60(2H, m), 4.02(2H, t, J=5.1Hz), 6.02(2H, s), 6.66-6.88(1H, m), 7.16(2H, d, J=8.8Hz).
MS (LC, ESI+) : 392.09(MH+), 433.16(MHMeCN+).

Example 85

N-(2-{4-[1-(1,3-Benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (181.2mg, 90.1%) was prepared from 2-{4-[1-(1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethanamine obtained by Example 84 in a similar manner to that of Example 75.

1HNMR ($CDCl_3$) : δ 3.6(2H, td, J=5.0, 5.0Hz), 4.045(2H, t, J=5Hz), 4.5(2H, br-s), 5.095(1H, br-t, J=5Hz), 6.01(2H, s), 6.66(1H, s), 6.75-6.86(3H, m), 6.84(2H, d, J=8Hz), 7.16(2H, d, J=8Hz).
MS (LC, ESI+) : 435.08(MH+).

Example 86

tert-Butyl 2-({4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}amino)-2-oxoethylcarbamate

A mixture of 4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzylamine hydrochloride obtained by Example 57, N-tert-butoxycarbonyl-glycine, WSCD and 1-hydroxybenzotriazole hydrate in triethylamine and dichloromethane was stirred at room temperature.

After stirring for 15hrs, the reaction mixture was poured onto

water and chloroform. The aqueous layer was separated and extracted with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel and crystallized to give the target compound (93.5mg, 88.9%).

1HNMR ($CDCl_3$) : δ 1.43(9H, s), 3.82(3H, s), 3.82-3.85(2H, m), 4.475(2H, d, J=6Hz), 6.71(1H, s), 6.87(2H, d, J=8Hz), 7.14-7.26(6H, m).
MS (ESI+) : 505(MH+).

Example 87

2-Amino-N-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}acetamide hydrochloride

The title compound (62.3mg, 82.9%) was prepared from tert-butyl 2-({4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}amino)-2-oxoethylcarbamate obtained by Example 86 in a similar manner to that of Example 74.

1HNMR (DMSO-d6) : δ 3.61(2H, s), 3.79(3H, s), 4.345(2H, d, J=6Hz), 7.005(2H, d, J=10Hz), 7.15(1H, s), 7.22-7.32(6H, m), 8.09(2H, br-s), 8.93(1H, br-t, J=6Hz).
MS (ESI+) : 405.33 (free, MH+).

Example 88

N-{4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}acetamide

To a solution of 4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzylamine hydrochloride obtained by Example 57 and triethylamine in dichloromethane was added dropwise acetyl chloride at 0℃.

After stirring at room temperature for 1hr, the mixture was quenched with saturated sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate (3 times). The combined organic layers were washed with 1N hydrochloric acid, water, and brine, dried over magnesium sulfate, and evaporated to give oil, which was purified with silica gel column chromatography (eluted with 50% ethyl acetate/n-hexane) to give oil. The oil was crystallized from a mixture of ethyl acetate and n-hexane at 50℃ to give the target compound (52.2mg, 69.3%) as a solid.

1HNMR ($CDCl_3$) : δ 2.04(3H, s), 3.83(3H, s), 4.435(2H, d, J=6Hz), 6.71(1H, s), 6.87(2H, d, J=8Hz), 7.15-7.26(6H, m).
IR (KBr) : 1647cm^{-1}.
MS (ESI+) : 412.1(M+Na).

Example 89
N-(2-{4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl)-1-methyl-1H-imidazole-4-sulfonamide

The title compound (72mg, 70.8%) was prepared from 2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanamine hydrochloride in a similar manner to that of Example 77.

1HNMR ($CDCl_3$) : δ 2.83(2H, t, J=8Hz), 3.26(2H, dt, J=6Hz), 3.75(3H, s), 3.83(3H, s), 5.005(1H, t, J=6Hz), 6.7(1H, s), 6.88(2H, d, J=8Hz), 7.13(4H, s), 7.22(2H, d, J=8Hz), 7.45-7.47(2H, m).
MS (ESI+) : 528.1 (MNa+).

Example 90
N-((1R)-2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}-1-methylethyl)urea

To a solution of (1R)-2-{4-[1-(4-methoxyphenyl)-3-(trifluorome

thyl)-1H-pyrazol-5-yl]phenoxy}-1-methylethanamine hydrochloride in dichloromethane was added triethylamine and trimethylsilyl isocyanate at 0℃.

After stirring for 5hrs, the mixture was quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure to give oil, which was purified with preparative thin layer chromatography (1mm, ethyl acetate) to give oil. The oil was crystallized from a mixture of isopropyl ether, ethyl acetate, and n-hexane to give the target compound as a white solid (22.8mg, 88.1%).

1HNMR ($CDCl_3$) : δ 1.29(3H, d, J=8Hz), 3.82(3H, s), 3.87-3.94(2H, m), 4.07-4.19(1H, m), 4.51(2H, s), 4.87(1H, d, J=8Hz), 6.67(1H, s), 6.8-6.89(4H, m), 7.12(2H, d, J=8Hz), 7.215(2H, d, J=10Hz).
MS (ESI+) : 435.3 (MH+), 476.3(MH+MeCN).

Example 91

N-(2-{4-[1-(6-Methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (130mg, 71.8%) was prepared from 2-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethanamine dihydrochloride in a similar manner to that of Example 77.

1HNMR ($CDCl_3$) : δ 3.03(3H, s), 3.555(2H, dt, J=5, 5Hz), 3.94(3H, s), 4.115(2H, t, J=5Hz), 4.785(1H, br-t, J=5Hz), 6.71(1H, s), 6.76(1H, d, J=8Hz), 6.85(2H, d, J=8Hz), 7.16(2H, d, J=8Hz), 7.555(2H, dd, J=8, 2Hz), 8.085(1H, d, J=2Hz).
MS (ESI+) : 479.1 (M+Na)+.

Example 92

4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenol

A mixture of 4-methoxy-1-(4,4,4-trifluoro-3-oxobutanoyl)benzene (5.0g) and p-hydroxyphenyl hydrazine hydrochloride (3.59g) in acetic acid (30ml) was stirred at room temperature.

After stirring for 15hrs, toluene and water was added. The aqueous layer was separated and extracted twice with toluene. The combined organic layer was washed with water (twice) and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel to give the target compound (4.88g, 71.9%) as crystals.

1HNMR($CDCl_3$) : δ 3.80(3H, s), 6.68(1H, s), 6.72(2H, d, J=8.8Hz), 6.83(2H, d, J=8.8Hz), 7.12(2H, d, J=8.8Hz), 7.13(2H, d, J=8.8Hz).
MS (ESI+) : m/z 357 (M+Na).

Example 93

2-{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethanol

A suspension of 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenol obtained by Example 92 (500mg), potassium carbonate (1.24g), potassium iodide (1.49g), and 2-chloro-1-ethanol (0.60ml) was stirred at 80℃ for 5hrs.

After cooling, the reaction mixture was poured into water. The mixture was extracted twice with ethyl acetate, washed with water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel to give the target compound (545mg, 96.4%).

1H NMR ($CDCl_3$) : δ 2.03(1H, t, J=5.8Hz), 3.81(3H, s), 3.94-4.01(2H, m), 4.09(2H, dd, J=3.5 ,4.6Hz), 4.52(3H, s), 6.68(1H, s), 6.84(2H,

d, J=8.9Hz), 6.89(2H, d, J=9Hz), 7.13(2H, d, J=8.9Hz), 7.24(2H, d, J=9Hz).

MASS (ESI+) : m/z 401 (M+Na).

Example 94

{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}acetonitrile

A suspension of 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenol obtained by Example 92 (2.0g), potassium carbonate (992mg), potassium iodide (993mg), and chloroacetonitrile (0.57 ml) was stirred at 80℃ for 4hrs.

After cooling, the reaction mixture was poured into water. The mixture was extracted twice with ethyl acetate, washed with water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel to give the target compound (1.75g, 78.3%) as an oil.

1H NMR ($CDCl_3$) : δ 3.81(3H, s), 4.79(2H, s), 6.69(1H, s), 6.86(2H, d, J=8.8Hz), 6.96(2H, d, J=9Hz), 7.14(2H, d, J=8.8Hz), 7.31(2H, d, J=9Hz).

MS (APCI+) : m/z 374 (M+1).

Example 95

tert-Butyl 2-{4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethylcarbamate

The title compound (420mg, 21%) was prepared from 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenol obtained by Example 92 in a similar manner to that of Example 73.

1H NMR ($CDCl_3$) : δ 1.46(9H, s), 3.501-3.58(2H, m), 4.02(2H, t, J=5.

1Hz), 4.99(1H, br-s), 6.67(1H, s), 6.84(2H, d, J=8.9Hz), 6.85(2H, d, J=9Hz), 7.13(2H, d, J=8.9Hz), 7.23(2H, d, J=9Hz).
MS (ESI+) : m/z 500 (M+Na).

Example 96

2-{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethanamine hydrochloride

The title compound (0.35g, 96.2%) was prepared from tert-butyl 2-{4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethylcarbamate obtained by Example 95 in a similar manner to that of Example 74.

1H NMR ($CDCl_3$+CD_3OD) : δ 3.2-3.5(4H, m), 3.81(3H, s), 4.2-4.35(2H, m), 6.70(1H, s), 6.84(2H, d, J=8.6Hz), 6.95(2H, d, J=8.6Hz), 7.13(2H, d, J=8.6Hz), 7.25(2H, d, J=8.6Hz).
MS (ESI+) : m/z 378 (M-Cl).

Example 97

N-(2-{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethyl)methanesulfonamide

To a solution of 2-{4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethanamine hydrochloride obtained by Example 96 (100mg) in dichloromethane (5ml) and triethylamine (0.1ml) was added dropwise methanesulfonyl chloride (38μl) at room temperature.

After stirring for 2hrs, the reaction mixture was partitioned between chloroform and water. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water and brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified with high performanced thin layer

chromatography to give the target compound (35mg, 31.8%) as crystals.

1H NMR ($CDCl_3$) : δ 3.03(3H, s), 3.56(2H, dt, J=5 ,5.7Hz), 3.81(3H, s), 4.11(2H, t, J=5Hz), 4.82(1H, t, J=5.7Hz), 6.68(1H, s), 6.85(2H, d, J=7.9Hz), 6.85(2H, d, J=8.7Hz), 7.13(2H, d, J=8.7Hz), 7.24(2H, d, J=7.9Hz).

MS (ESI+) : m/z 478 (M+Na).

Example 98

N-(2-{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethyl)urea

To a solution of 2-{4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethanamine hydrochloride obtained by Example 96 (200mg) in water (10ml) and ethanol (5ml) was added sodium cyanate (314mg) at room temperature.

After stirring for 15hrs, the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatography by high performanced thin layer chromatography (chloroform:methanol=8:1) to give the target compound (0.148g, 72.8%).

1H NMR ($CDCl_3$) : δ 3.60(2H, dt, J=5.6, 5.0Hz), 3.81(3H, s), 4.04(2H, t, J=5.0Hz), 4.50(2H, br-s), 5.12(1H, t, J=5.6Hz), 6.68(1H, s), 6.84(2H, d, J=8.8Hz), 6.85(2H, d, J=8.9Hz), 7.13(2H, d, J=8.8Hz), 7.22(2H, d, J=8.9Hz).

MS (ESI+) : m/z 443 (M+Na).

Example 99

N-(2-{4-[3-(Difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]ph

enyl}ethyl)-2-hydroxyethanesulfonamide

To a solution of 2-(2-{4-[1-(4-methoxyphenyl)-3-difluoromethyl-1H-pyrazol-5-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione in acetonitrile was added hydrazine monohydrate.

After stirring at 60℃ overnight, the mixture was filtered. And the filtrate was evaporated to give 2-{4-[1-(4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanamine as an orange oil.

To a solution of the oil and triethylamine in chloroform was added 2-hydroxyethanesulfonyl chloride at room temperature.

After stirring for 1hr, the reaction mixture was poured onto water and chloroform. The aqueous layer was separated and extracted with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel and crystalized to give the target compound (220mg, 76.1%).

1H NMR ($CDCl_3$) : δ 2.875(2H, t, J=7Hz), 2.91-3.19(2H, m), 3.395(2H, dt, J=6Hz), 3.83(3H, s), 3.985(2H, t, J=5Hz), 4.44(1H, br-t, J=6Hz), 6.7(1H, s), 6.765(1H, t, J=55Hz), 6.875(2H, d, J=10Hz), 7.12(6H, s).

MS (ESI+) : 452.19(MH+).

In order to illustrate the usefulness of the object compounds (I), the pharmacological test data of the compounds (I) are shown i n the following.

[A] ANALGESIC ACTIVITY :

Effect on adjuvant arthritis in rats :

(i) Test Method :

Analgesic activity of a single dose of agents in arthritic rats was studied.

Arthritis was induced by injection of 0.5 mg of Mycobacterium tuberculosis (Difco Laboratories, Detroit, Mich.) in 50μl of liquid paraffin into the right hind footpad of Lewis rats aged 7 weeks. Arthritic rats were randomized and grouped (n=10) for drug treatment based on pain threshold of left hind paws and body weight on day 22.

Drugs (Test compounds) were administered and the pain threshold was measured 2hrs after drug administration. The intensity of hyperalgesia was assessed by the method of Randall - Selitto. The mechanical pain threshold of the left hind paw (uninjected hind paw) was determined by compressing the ankle joint with a balance pressure apparatus (Ugo Basile Co.Ltd., Varese, Italy). The threshold pressure of rats squeaking or struggling was expressed in grams. The threshold pressure of rats treated with drugs was compared with that of non-treated rats. A dose showing the ratio of 1.5 is considered to be the effective dose.

(ii) Test Results:

Test compound (Example No.)	Dose (mg/kg)	The coefficient of analgesic
23	3.2	>1.5
28	3.2	>1.5
61	3.2	>1.5

[B] Inhibiting activity against COX-I and COX-II

(Whole Blood Assay):

(i) Test Method :

Whole blood assay for COX-I

Fresh blood was collected by syringe without anticoagulants from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

500μl Aliquots of human whole blood were immediately incubated with 2μl of either dimethyl sulfoxide vehicle or a test compound at final concentrations for 1hr at 37℃ to allow the blood to clot. Appropriate treatments (no incubation) were used as blanks. At the end of the incubation, 5μl of 250mM Indomethacin was added to stop the reaction. The blood was centrifuged at 6000 x g for 5min at 4℃ to obtain serum. A 100μl aliquot of serum was mixed with 400μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4℃ and was assayed for TXB_2 using an enzyme immunoassay kit according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of thromboxane B_2(TXB_2) production relative to control incubations containing dimethyl sulfoxide vehicle.

The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC_{50} value was calculated by least squares method.

Whole blood assay for COX-II

Fresh blood was collected in heparinized tubes by syringe from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

500μl aliquots of human whole blood were incubated with either 2μl dimethyl sulfoxide vehicle or 2μl of a test compound at final concentrations for 15 min at 37℃. This was followed by incubation

of the blood with 10μl of 5mg/ml lipopolysaccharide for 24hrs at 37℃ for induction of COX-II. Appropriate PBS treatments (no LPS) were used as blanks. At the end of the incubation, the blood was centrifuged at 6000Xg for 5 min at 4℃ to obtain plasma. A 100μl aliquot of plasma was mixed with 400μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000Xg for 5min at 4℃ and was assayed for prostaglandin E_2 (PGE_2) using a radioimmunoassay kit after conversion of PGE_2 to its methyl oximate derivative according to the manufacturer's procedure.

For a test compound, the results were expressed as percent inhibition of PGE_2 production relative to control incubations containing dimethyl sulfoxide vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC_{50} value was calculated by least squares method.

(ii) Test Results:

Test Compound (Example No.)	COX-I IC50 (μM)	COX-II IC50 (μM)
23	< 0.01	> 0.1
28	< 0.01	> 0.1
61	< 0.01	> 0.1

It appeared, from the above-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against COX, particularly a selective inhibiting activity against COX-I.

[C] Inhibiting activity on aggregation of platelet

(i) Methods

Preparation of platelet-rich plasma

Blood from healthy human volunteers was collected into plastic vessels containing 3.8% sodium citrate (1/10 volume). The subject had

no taken any compounds for at least 7days prior to blood collection. Platelet-rich plasma was obtained from the supernatant fraction of blood after centrifugation at 1200rpm. for 10min. Platelet-poor plasma was obtained by centrifugation of the remaining blood at 3000rpm for 10min.

Measurement of platelet aggregation

Platelet aggregation was measured according to the turbidimetric method with an aggregometer (Hema Tracer). In the cuvette, platelet-rich plasma was pre-incubated for 2min at 37℃ after the addition of compounds or vehicle. In order to quantify the inhibitory effects of each compound, the maximum increase in light transmission was determined from the aggregation curve for 7min after the addition of agonist. We used collagen as agonist of platelet aggregation in this study. The final concentration of collagen was 0.5μg/mL. The effect of each compound was expressed as percentage inhibition agonist-induced platelet aggregation compared with vehicle treatment. Data are presented as the mean ± S.E.M. for six experiments. The IC_{50} value was obtained by linear regression, and is expressed as the compound concentration required to produce 50% inhibition of agonist-induced platelet aggregation in comparison to vehicle treatment.

It appeared, from the above-mentioned Test Result, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against platelet aggregation. Therefore, the compound (I) or pharmaceutically acceptable salts thereof are useful for preventing or treating disorders induced by platelet aggregation, such as thrombosis.

Additionally, it was further confirmed that the compounds (I) of the present invention lack undesired side-effects of non-selective NSAIDs, such as gastrointestinal disorders, bleeding, renal toxicity, cardiovascular affection, etc.

As shown above, the object compound (I) or pharmaceutically acceptable salts thereof of this invention possesses COX inhibiting activity and possesses strong anti-inflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on.

The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing COX mediated diseases, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically.

More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and acute or chronic pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, scapulohumeral periarthritis, cervical syndrome, etc.]; lumbago; inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.]; inflammatory eye condition [e.g. conjunctivitis, etc.]; lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.]; condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varioloid, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.]; gingivitis; menorrhalgia; inflammation, pain and tumescence after operation or injury [pain after odontectomy, etc.] ; pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis,

Hodgkin's disease, Alzheimers disease, or the like.

Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

The object compound (I) and a salt thereof can be used for prophylactic and therapeutic treatment of arterial thrombosis, arterial sclerosis, ischemic heart diseases [e.g. angina pectoris (e.g. stable angina pectoris, unstable angina pectoris including imminent infarction, etc.), myocardial infarction (e.g. acute myocardial infarction, etc.), coronary thrombosis, etc.], ischemic brain diseases [e.g. cerebral infarction (e.g. acute cerebral thrombosis, etc.), cerebral thrombosis (e.g. cerebral embolism, etc.), transient cerebral ischemia (e.g. transient ischemic attack, etc.), cerebrovascular spasm after cerebral hemorrhage(e.g. cerebrovascular spasm after subarachnoid hemorrhage, etc.), etc.], pulmonary vascular diseases (e.g. pulmonary thrombosis, pulmonary embolism etc.), peripheral circulatory disorder [e.g. arteriosclerosis obliterans, thromboangiitis obliterans (i.e. Buerger's disease), Raynaud's disease, complication of diabetes mellitus (e.g. diabetic angiopathy, diabetic neuropathy, etc.), phiebothrombosis (e.g. deep vein thrombosis, etc.), etc.], complication of tumors (e.g. compression thrombosis), abortion [e.g. placental thrombosis, etc.], restenosis and reocclusion [e.g. restenosis and/or reocclusion after percutaneous transluminal coronary angioplasty (PTCA), restenosis and reocclusion after the administration of thrombolytic drug (e.g. tissue plasminogen activator (TPA), etc.)], thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation [e.g. surgery (e.g. open heart surgery, pump-oxygenator, etc.) hemodialysis, etc.] or transplantation, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia, essential thrombocytosis, inflammation (e.g. nephritis, etc.), immune diseases, atrophic thrombosis, creeping

thrombosis, dilation thrombosis, jumping thrombosis, mural thrombosis, etc..

The object compound (I) and a salt thereof can be used for the adjuvant therapy with thrombolytic drug (e.g. TPA, etc.) or anticoagulant (e.g. heparin, etc.).

And, the compound (I) is also useful for inhibition of thrombosis during extra corporeal circulation such as dialysis.

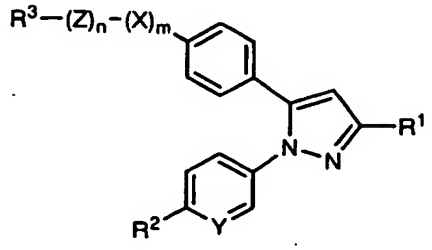
Particularly, the following diseases are exemplified: pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis, etc; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury; etc..

And on the commercial package comprising the pharmaceutical composition mentioned above, the matter, which states above mentioned effects, may be written.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (I):



(I)

wherein R^1 is (lower)alkyl,
(lower)alkyl substituted with halogen,
(lower)alkyl substituted with hydroxy,
(lower)alkenyl,
(lower)alkoxy,
cycloalkyl,
cyano,
amino,
halogen,
hydroxy,
[di(lower)alkyl]amino,
[(lower)alkoxy]carbonyl,
(lower)alkanoyl,
(cycloalkyl)carbonyl, or
[N,N-di(lower)alkyl]carbamoyl;

R^2 is (lower)alkoxy,
halogen,
(lower)alkyl
(lower)alkyl substituted with amino,
(lower)alkyl substituted with (carbamoyl)amino,
(lower)alkyl substituted with
[(lower)alkyl]sulfonamide,
cyano,
hydroxy,

[aryl(lower)alkyl]oxy,
[(lower)alkanoyl]oxy,
[(lower)alkylene]dioxy,
(lower)alkoxy substituted with hydroxy,
(lower)alkoxy substituted with cyano,
(lower)alkoxy substituted with amino,
(lower)alkoxy substituted with [(lower)alkoxy]carbonylamino,
(lower)alkoxy substituted with [(lower)alkyl]sulfonamide, or
(lower)alkoxy substituted with (carbamoyl)amino;

R^3 is hydrogen,
amino,
[(lower)alkokycarbonyl]amino,
[(lower)alkyl]sulfonamide,
(carbamoyl)amino,
aryl,
heteroaryl,
(lower)alkoxy,
hydroxy,
[(lower)alkyl]sulfonyloxy,
(lower)alkyl,
(lower)alkyl substituted hydroxy,
(lower)alkyl substituted with amino,
(lower)alkyl substituted with [(lower)alkoxycarbonyl]amino,
cyano,
(lower)alkanoyl, or
(lower)alkanoyl substituted with halogen;

X is O, S or (lower)alkylene;

Y is CH or N;

Z is (lower)alkylene, amide or sulfonamide;

m is 0 or 1; and

n is 0 or 1;

or salts thereof.

2. A pharmaceutical composition comprising the compound (I) or its salts of Claim 1, as an active ingredient, in association with a pharmaceutically non-toxic carrier or excipient.

3. A compound of Claim 1 for use as a medicament

4. A method for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases which comprises administering an effective amount of the compound or its salts of Claim 1 to human beings or animals.

5. Use of the compound of Claim 1 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases in human beings or animals.

6. The analgesic agent comprising the compound of Claim 1, which is usable for treating and/or preventing pains caused by or associated with acute or chronic inflammations without causing gastrointestinal disorders.

7. The analgesic agent of Claim 6, which is usable for treating or preventing pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, or juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after

operation or injury without causing gastrointestinal disorders.

8. A commercial package comprising the pharmaceutical composition containing the compound (I) identified in Claim 1 and a written matter associated therewith, wherein the written matter states that the compound (I) can or should be used for preventing or treating inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases.

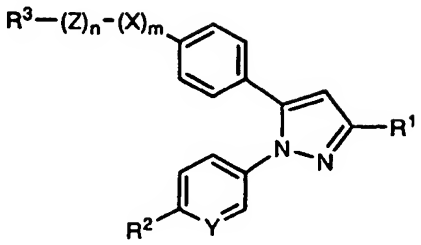
DATED this 29th day of April, 2003

Fujisawa Pharmaceutical Co., Ltd.

By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

A B S T R A C T

A compound of the formula (I):



(I)

wherein R^1 is (lower)alkyl, etc.;

R^2 is (lower)alkoxy, etc.;

R^3 is hydroxy, etc.;

X is O, S or (lower)alkylene;

Y is CH or N;

Z is (lower)alkylene, amide or sulfonamide;

m is 0 or 1; and

n is 0 or 1;

or salts thereof.

Customer Number

22850

703- 413-3000

SERIAL NO.: 101 706,999

FILING DATE: November 14, 2003